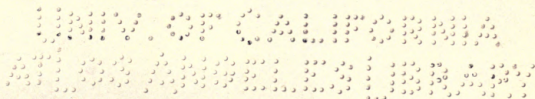


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A LABORATORY MANUAL AND TEXT-BOOK

of

EMBRYOLOGY



By

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PREFACE TO THE THIRD EDITION

THE rapid exhaustion of the second edition of this text has hastened the appearance of the present volume. Its contents have again been subjected to a systematic revision which affects each chapter more or less profoundly. The addition of much new material and the recasting and modifying of former descriptions will result, it is hoped, in a two-fold gain, without appreciably increasing the size of the book.

L. B. A.

CHICAGO, ILL.,
August, 1920.

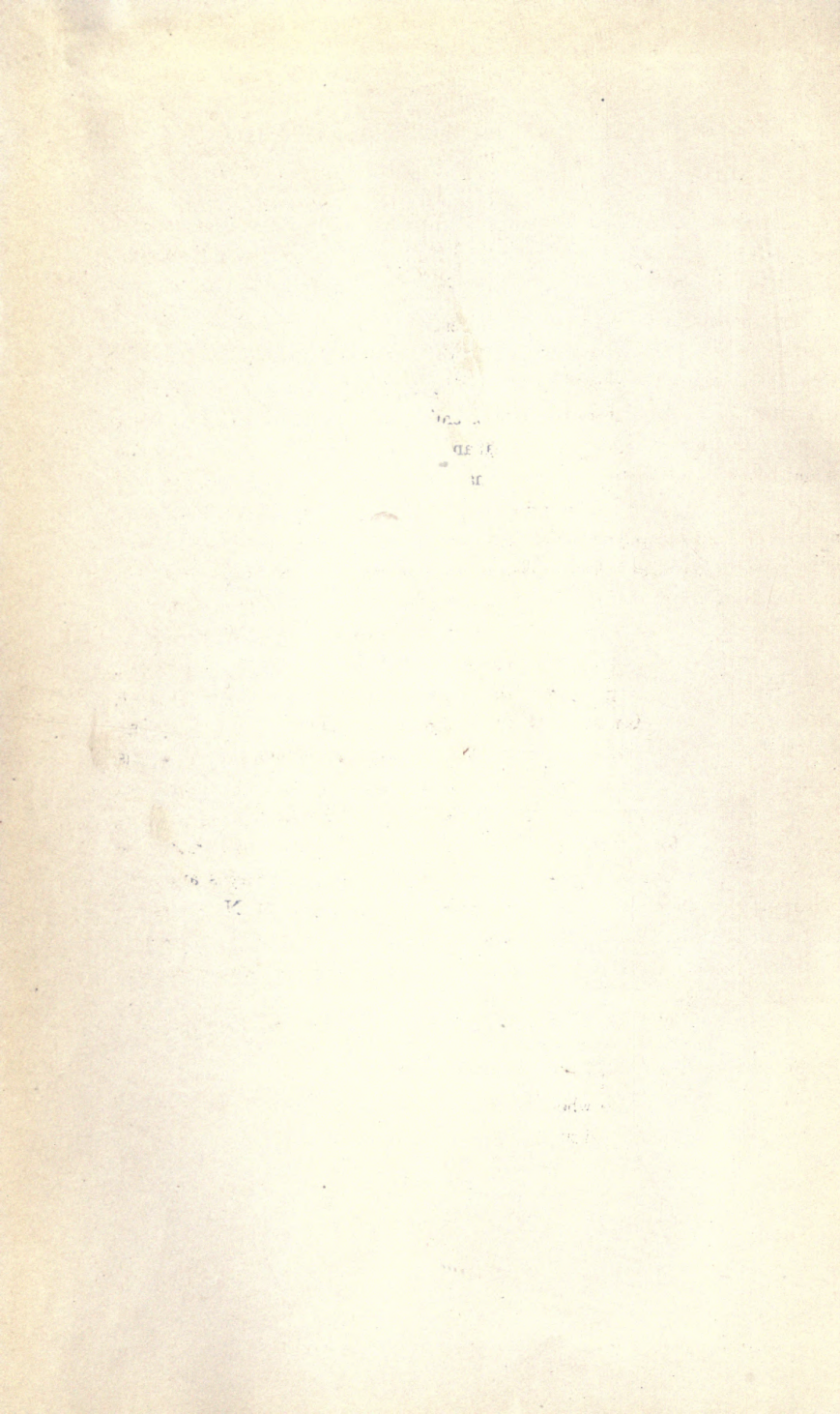
PREFACE TO THE SECOND EDITION

THE untimely death of Professor Prentiss has made necessary the transfer of his 'Embryology' into other hands. In this second edition, however, the general plan and scope of the book remain unchanged although the actual descriptions have been extensively recast, rewritten, and rearranged. A new chapter on the Morphogenesis of the Skeleton and Muscles covers briefly a subject not included hitherto. Forty illustrations replace or supplement certain of those in the former edition.

In preparing the present manuscript a definite attempt has been made to render the descriptions as clear and consistent as is compatible with brevity and accuracy. It has likewise been essayed to evaluate properly the embryological contributions of recent years, and, by incorporating the fundamental advances, to indicate the trend of modern tendencies. Since no page remains in its entirety as originally penned by Professor Prentiss, the reviser must assume full responsibility for the subject-matter as it now stands.

It is hoped that those who read this text will co-operate with the writer by freely offering criticisms and suggestions.

L. B. A.



PREFACE

THIS book represents an attempt to combine brief descriptions of the vertebrate embryos which are studied in the laboratory with an account of human embryology adapted especially to the medical student. Professor Charles Sedgwick Minot, in his laboratory textbook of embryology, has called attention to the value of dissections in studying mammalian embryos and asserts that "dissection should be more extensively practised than is at present usual in embryological work." The writer has for several years experimented with methods of dissecting pig embryos, and his results form a part of this book. The value of pig embryos for laboratory study was first emphasized by Professor Minot, and the development of my dissecting methods was made possible through the reconstructions of his former students, Dr. F. T. Lewis and Dr. F. W. Thyng.

The chapters on human organogenesis were partly based on Keibel and Mall's Human Embryology. We wish to acknowledge the courtesy of the publishers of Kollmann's Handatlas, Marshall's Embryology, Lewis-Stöhr's Histology and McMurrich's Development of the Human Body, by whom permission was granted us to use cuts and figures from these texts. We are also indebted to Professor J. C. Heisler for permission to use cuts from his Embryology, and to Dr. J. B. De Lee for several figures taken from his "Principles and Practice of Obstetrics." The original figures of chick, pig and human embryos are from preparations in the collection of the anatomical laboratory of the Northwestern University Medical School. My thanks are due to Dr. H. C. Tracy for the loan of valuable human material, and also to Mr. K. L. Vehe for several reconstructions and drawings.

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TEXT-BOOK OF EMBRYOLOGY

INTRODUCTION

THE study of human embryology deals with the development of the individual from the origin of the germ cells to the adult condition. To the medical student human embryology is of primary importance because it affords a comprehensive understanding of gross anatomy. It is on this account that only recently a prominent surgeon has recommended a thorough study of embryology as one of the foundation stones of surgical training. Embryology not only throws light on the normal anatomy of the adult, but it also explains the occurrence of many anomalies and monsters, and the origin of certain pathological changes in the tissues. Obstetrics is essentially applied embryology. From the theoretical side, embryology is the key with which we may unlock the secrets of heredity, the determination of sex, and, in part, of organic evolution.

There is, unfortunately, a view current among graduates in medicine that the field of embryology has been fully reaped and gleaned of its harvest. On the contrary, much productive ground is as yet unworked, and all *well-preserved* human embryos are of value to the investigator. Only through the co-operation of clinicians in collecting and preserving embryos will our ignorance of early human development be rectified. At present, practically nothing is known of the maturing ovum, while of fertilization, cleavage, and the formation of the germ layers we are entirely in the dark. *Aborted embryos and those obtained by operation in case of either normal or ectopic pregnancies should always be saved and preserved at once by immersing them intact in 10 per cent formalin or in Zenker's fluid.*

Historical.—The science of modern embryology is comparatively new, originating with the use of the compound microscope and developing with the improvement of microscopical technique. Aristotle (384–322 B. C.), however, centuries before had followed the general development of the chick day by day. The belief that slime and decaying matter was capable of giving rise to living animals, as asserted by Aristotle, was disproved by Redi (1668).

A few years after Harvey and Malpighi had published their studies on the chick embryo, Leeuwenhoek reported the discovery of the spermatozoön by Ham in 1677. At this period it was believed either that fully

formed animals existed in miniature in the egg, needing only the stimulus of the spermatozoön to initiate development, or that similarly preformed bodies, male and female, constituted the spermatozoa and that these merely enlarged within the ovum. According to this doctrine of *preformation* all future generations were likewise encased, one inside the sex cells of the other, and serious computations were made as to the probable number of progeny (200 million) thus present in the ovary of Mother Eve, at the exhaustion of which the human race would end! Dalenpatius (1699) believed that he had observed a minute human form in the spermatozoön.

The preformation theory was strongly combated by Wolff (1759) who saw that the early chick embryo was differentiated gradually from unformed living substance. This theory, known as *epigenesis*, was proved correct when, in 1827, von Baer discovered the mammalian ovum and later demonstrated the germ layers of the chick embryo.

About twenty years after Schleiden and Schwann (1839) had shown the cell to be the structural unit of the organism, the ovum and spermatozoön were recognized as true cells. O. Hertwig, in 1875, was the first to observe and appreciate the events of fertilization. Henceforth all multicellular organisms were believed to develop each from a single fertilized ovum, which by continued cell division eventually gives rise to the adult body, that of man, it is estimated, containing 26 million million cells. In the case of vertebrates, the segmenting ovum differentiates first *three primary germ layers*. The cells of these layers are modified in turn to form *tissues*, such as muscle and nerve, of which the various *organs* are composed, and the organs together constitute the *organism*, or adult body.

Primitive Segments—Metamerism.—In studying vertebrate embryos we shall identify and constantly refer to the *primitive segments*, or *metameres*. These segments are homologous to the serial divisions of an adult earth worm's body, divisions which, in the earth worm, are identical in structure, each containing a *ganglion* of the nerve cord, a muscle segment, or *myotome*, and pairs of blood vessels and nerves. In vertebrate embryos the primitive segments are known as *mesodermal segments*, or *somites*. Each pair gives rise to a vertebra, to a pair of myotomes, or muscle segments, and to paired vessels; each pair of mesodermal segments is supplied by a pair of spinal nerves, consequently the adult vertebrate body is segmented like that of the earth worm. As a worm grows by the formation of new segments at its tail-end, so the metameres of the vertebrate embryo begin to form in the head and are added tailward. There is this difference between the segments of the worm and the vertebrate embryo: The segmentation of the worm is complete, while that of the vertebrate is incomplete ventrally.

GROWTH AND DIFFERENTIATION OF THE EMBRYO

A multicellular embryo develops by the division of the fertilized ovum to form daughter cells. These are at first quite similar in structure, and, if separated, in some animals each may develop into a complete embryo (sea urchin; certain vertebrates). The further development of the embryo depends: (1) upon the multiplication of its cells by division; (2) upon the growth in size of the individual cells; (3) upon changes in their form and structure.

The first changes in the form and arrangement of the cells give rise to three definite plates, or *germ layers*, which are termed from their positions the *ectoderm* (outer skin), *mesoderm* (middle skin) and *entoderm* (inner skin). Since the ectoderm covers the body, it is primarily protective in function, but it also gives rise to the nervous system, through which sensations are received from the outer world. The *entoderm*, on the other hand, lines the digestive canal and is from the first nutritive in function. The *mesoderm*, lying between the other two layers, naturally performs the functions of circulation, of muscular movement, and of excretion; it also gives rise to the skeletal structures which support the body. While all three germ layers form definite sheets of cells known as *epithelia*, the mesoderm takes also the form of a diffuse network of cells, the *mesenchyma*.

The Anlage.—This German word, which lacks an entirely satisfactory English equivalent, is a term applied to the first discernible cell, or aggregation of cells, which is destined to form any distinct part or organ of the embryo. In the broad sense the fertilized ovum is the anlage of the entire adult organism; furthermore, in the early cleavage stages of certain embryos it is possible to recognize single cells or cell groups from which definite structures will indubitably arise. The term anlage, however, is more commonly applied to the primordia that differentiate from the various germ layers. Thus the epithelial thickening over the optic vesicle is the anlage of the lens.

Differentiation of the Embryo.—The developing embryo exhibits a progressively complex structure, the various steps in the production of which occur in orderly sequence. There may be recognized in development a number of component mechanical processes which are used repeatedly by the embryo. The general and fundamental process conditioning differentiation is *cell multiplication*, and the subsequent growth of the daughter cells. The more important of the specific developmental processes are the following: (1) *cell migration*; (2) *localized growth*, resulting in *enlargements* and *constrictions*; (3) *cell aggregation*, forming (a) *cords*, (b) *sheets*, (c) *masses*; (4) *delamination*, that is, the splitting of single sheets

into separate layers; (5) *folds*, including circumscribed folds which produce (a) *evaginations*, or out-pocketings, as the intestinal villi, (b) *invaginations* or in-pocketings, as the intestinal glands.

The production of folds, including evaginations and invaginations, due to unequal rapidity of growth, is the chief factor in moulding the organs and hence the general form of the embryo.

Differentiation of the Tissues.—The cells of the germ layers that form organic anlagen may be at first alike in structure. Thus the evagination which forms the anlage of the arm is composed of a single layer of like ectodermal cells, surrounding a central mass of diffuse mesenchyma (Fig. 136). Gradually the ectodermal cells multiply, change their form and structure, and give rise to the layers of the epidermis. By more profound structural changes the mesenchymal cells also are transformed into the elements of connective tissue, tendon, cartilage, bone, and muscle, aggregations of modified cells which are known as *tissues*. The development of modified tissue cells from the undifferentiated cells of the germ layers is known as *histogenesis*. During histogenesis the structure and form of each tissue cell are adapted to the performance of some special function or functions. Cells which have once taken on the structure and functions of a given tissue cannot give rise to cells of any other type. In tissues like the epidermis, certain cells retain their primitive embryonic characters throughout life, and, by continued cell division, produce new layers of cells which are later cornified. In other tissues all of the cells are differentiated into the adult type, after which no new cells are formed. This takes place in the case of the nervous elements of the central nervous system.

Throughout life, tissue cells are undergoing retrogressive changes. In this way the cells of certain organs like the thymus gland and mesonephros degenerate and largely disappear. The cells of the hairs and the surface layer of the epidermis become cornified and eventually are shed. Thus, normally, tissue cells may constantly be destroyed and replaced by new cells.

Cytomorphosis.—This series of changes—an embryonic (undifferentiated) stage; progressive functional specialization; gradual degeneration; death and removal—which tissue cells experience is known by the term *cytomorphosis*.

Postnatal Development.—Development does not cease at birth, but continues until the adult stage is attained. Birth, itself, initiates anatomical and physiological changes of profound influence on the body. Throughout the growth period, with its uneven but steadily slowing growth rate, comes a remoulding of the shape of the body and its parts. During this time most of the organs lose in relative weight; the skeleton

and especially the muscles gain; the pancreas, digestive tube, and lungs are little affected.

Continuity of the Germ Plasm.—According to this important conception of Weismann, the body-protoplasm, or soma, and the reproductive-protoplasm differ fundamentally. The germinal material is a legacy that has existed since the beginning of life, from which representative portions are passed on intact from one generation to the next. Around this germ plasm there develops in each successive generation a short-lived body, or soma, which serves as a vehicle for insuring the transmission and perpetuation of the former. The reason, therefore, why offspring resembles parent is because each develops from portions of the same stuff.

The Law of Biogenesis.—Of great theoretical interest is the fact, constantly observed in studying embryos, that the individual in its development repeats hastily and incompletely the evolutionary history of its own species. This *law of recapitulation* was first stated clearly by Müller in 1863 and was termed by Haeckel the *law of biogenesis*. In accordance with it, the fertilized ovum is compared to a unicellular organism like the *Amœba*; the blastula is supposed to represent an adult *Volvox* type; the gastrula, a simple sponge; the segmented embryo a worm-like stage, and the embryo with gill slits may be regarded as a fish-like stage. Moreover, the blood of the human embryo in development passes through stages in which its corpuscles resemble in structure those of the fish and reptile; the heart is at first tubular, like that of the fish, and the arrangement of blood vessels is equally primitive; the kidney of the embryo is like that of the amphibian, as are also the genital ducts. Many other examples of this law may readily be observed.

Some apparently useless structures appear during development, perfunctorily reminiscent of ancestral conditions; certain other parts, of use to the embryo alone, are later replaced by better adapted, permanent organs. Representatives of either of these types may eventually disappear or they may persist throughout life as rudimentary organs; more than a hundred of the latter have been listed for man. Still other ancestral organs abandon their provisional embryonic function, yet are retained in the adult and utilized for new purposes.

Methods of Study.—Human embryos not being available for individual laboratory work, the embryos of the lower animals which best illustrate certain points are employed instead. Thus the germ cells of *Ascaris*, a parasitic round worm, are used to demonstrate the phenomena of mitosis and maturation; early stages of echinoderms, or of worms, are frequently used to demonstrate the cleavage of the ovum and the development of the blastula and gastrula; the chick embryo affords convenient material for the study of the early vertebrate embryo and the formation of

the germ layers and embryonic membranes, while the structure of a mammalian embryo, similar to that of the human embryo, is best observed in the readily-procured embryos of the pig. An idea of the anatomy of embryos is obtained first by examining the exterior of whole embryos and studying dissections and reconstructions of them. Finally, each embryo is studied in serial sections, the level of each section being determined by comparing it with figures of the whole embryo.

Along with his study of the embryos in the laboratory, the student should do a certain amount of supplementary reading. Only the gist of human organogenesis is contained in the following chapters. A very complete bibliography of the subject is given in Keibel and Mall's "Human Embryology," to which the student is referred. Below are given the titles of some of the more important works on vertebrate and human embryology, to which the student is referred and in which supplementary reading is recommended.

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CHAPTER I

THE GERM CELLS: MITOSIS, MATURATION AND FERTILIZATION

THE GERM CELLS

THOSE animals, whose offspring reach maturity with reasonable surety (as the result of internal fertilization and postnatal care), produce fewer germ cells, especially ova, than those that leave fertilization to chance and development to hazard. The codfish produces 10 million eggs in a breeding period, a sea urchin 20 million; in certain mammals and birds only a single egg is matured, yet the stock of each remains constant.

The highly differentiated human organism, like all other vertebrates and most invertebrates, develops from the union of two germ cells, the ovum and spermatozoön.

The Ovum.—The female germ cell, or ovum, is a typical animal cell produced in the ovary. It is nearly spherical in form and possesses a *nucleus* with *nucleolus*, *chromatin network*, and *nuclear membrane* (Figs. 1 and 2). The nucleus is essential to the life, growth, and reproduction of the cell. The function of the nucleolus is unknown; the chromatin probably bears the hereditary qualities of the cell. The *cytoplasm* of the ovum is distinctly granular, containing more or less numerous *yolk granules*, *mitochondria*, and rarely a minute *centrosome*. The yolk granules, containing a fatty substance termed *lecithin*, furnish nutrition for the early development of the embryo. A relatively small amount of yolk is found in the ova of the higher mammals, since the embryo develops within the uterine wall of the mother and is nourished by it. A much larger amount occurs in the ova of fishes, amphibia, reptiles, birds, and the primitive mammalia, the eggs of which are laid and develop outside of the body. The so-called yolk of the hen's egg (Fig. 3) is the ovum proper and its yellow color is due to the large amount of lecithin which it contains.

Ova become surrounded by protective membranes, or envelopes. The *vitelline membrane*, secreted by the egg itself, is a primary membrane (Fig. 2). The follicle cells about the ovum usually furnish other secondary membranes, such as the *zona pellucida*. In lower vertebrates tertiary membranes may be added as the egg passes through the oviduct and uterus—the albumen and shell of the hen's egg (Fig. 3) or the jelly of the frog's egg are of this type.

The human ovum is of relatively small size, measuring from 0.22 to 0.25 mm. in diameter (Fig. 1). The cytoplasm is surrounded by a thick,

radially striated membrane, the *zona pellucida*. The striated appearance of the *zona pellucida* is said to be due to fine canals which penetrate it

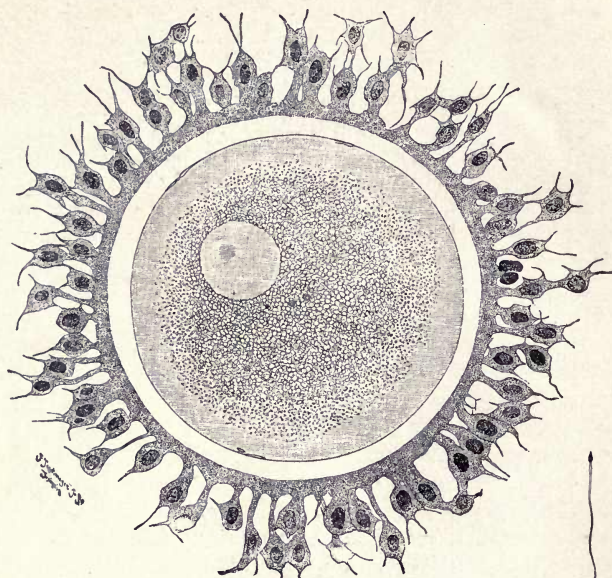


FIG. 1.—Human ovum, two-thirds the mature size, examined fresh in the liquor folliculi (Waldeyer). $\times 415$. The *zona pellucida* is seen as a clear girdle surrounded by the cells of the corona radiata. Yolk granules occupy a central region of the cytoplasm and enclose the nucleus and nucleolus. At the right is a spermatozoön correspondingly enlarged.

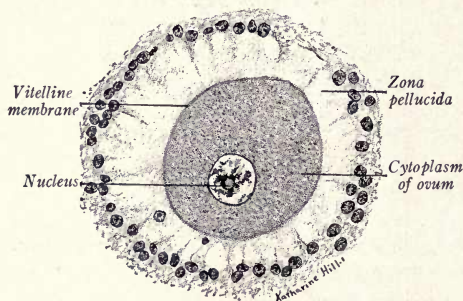


FIG. 2.—Ovum of monkey. $\times 430$.

and through which nutriment is transferred from smaller follicle cells to the ovum during its growth within the ovary. The origin and growth of the ovum within the ovary (oögenesis) are described on pp. 216-218.

For the present it is sufficient to state that each growing ovum is at first surrounded by small nutritive cells known as *follicle cells*. These increase in number during the growth of the ovum until several layers are formed (Fig. 229). A cavity appearing between these cells becomes filled with

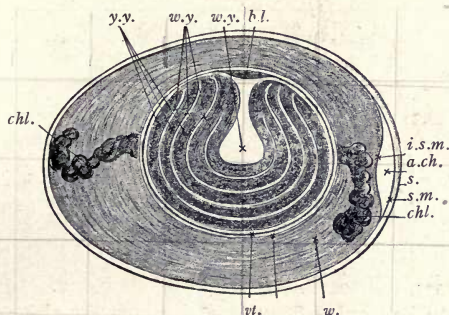


FIG. 3.—Diagrammatic longitudinal section of an unincubated hen's egg (Allen Thomson in Heisler). *bl.*, Blastoderm; *w.y.*, white yolk, which consists of a central flask-shaped mass, and of concentric layers alternating with the yellow yolk (*y.y.*); *vt.*, vitelline membrane; *w.*, albumen; *chl.*, chalaza; *a.ch.*, air chamber; *i.s.m.*, inner, *s.m.*, outer layer of the shell membrane; *s.*, shell.

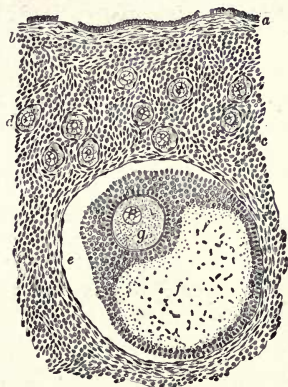


FIG. 4.—Section of human ovary (Piersol). *a*, Germinal epithelium; *b*, tunica albuginea; *c*, cortical stroma containing immature follicles; *d*, *e*, shrinkage space between theca and stratum granulosum of a well-advanced Graafian follicle; *f*, liquor folliculi; *g*, ovum surrounded by cumulus oöphorus.

fluid and thus forms a sac, the *vesicular (Graafian) follicle*, within which the ovum is eccentrically located (Figs. 4 and 230). The follicular cells immediately surrounding the ovum form the *corona radiata* (Fig. 1) when the ovum is set free.

Ovulation and Menstruation.—At birth, or shortly after, ova cease forming. The number at this time in both ovaries has been placed between 100,000 and 800,000. Cellular degeneration reduces this supply,



FIG. 5.—Uterine tube and ovary with mature Graafian follicle (Ribemont-Dessaignes).

until, at 18 years, the total is from 35,000 to 70,000. Of these, relatively few reach maturity, only about 200 ripe ova developing in each ovary during the thirty years of sexual activity. Several years after the meno-

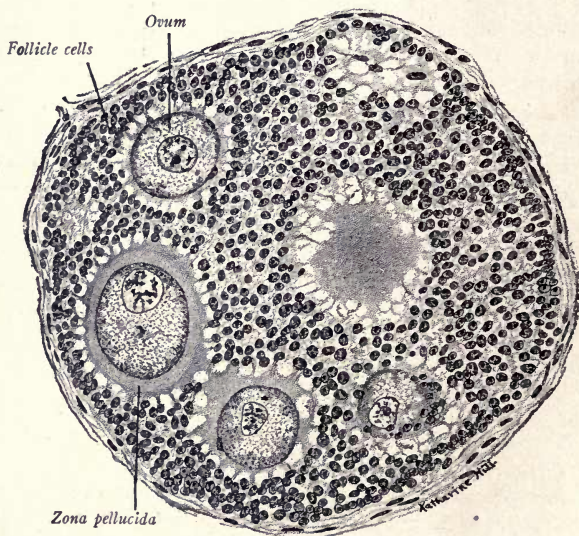


FIG. 6.—Immature follicle containing six ova. From the ovary of a young monkey. $\times 430$.

pause no more ova are to be found. When an ovum is ripe, the Graafian follicle is large and contains fluid, probably under vascular and muscular pressure. The ripe follicles form bud-like protuberances at the surface of

the ovary (Fig. 5) and at these points the ovarian wall has become very thin. At *ovulation*, that is, the bursting of the Graafian follicle and the discharge of the ovum, but one ovum is usually liberated. Several ova, however, may be produced in a single follicle in rare cases. Such multiple follicles have been observed in human ovaries and are of frequent occurrence in the monkey (Fig. 6).

The observations of various older workers (Leopold, Ravano and others) led Mall (1910) to conclude that they had "shown conclusively that ovulation and menstruation are usually synchronous." Since then, Meyer, Ruge, Schröder, Fraenkel, and Halban, utilizing better standardized corpora lutea as criteria, have presented evidence accepted by Grosser (1914) and Mall (1918) as proof that ovulation occurs most often between the fourth and fourteenth day after the menstrual onset. A survey of all the clinical data indicates that any such relation is at best very loose and that many ova are liberated without definite reference to the menstrual cycle. Moreover, in young girls ovulation may precede the inception of menstruation and it may occur in women during pregnancy or after the menopause.

The Spermatozoön.—The male cell, or spermatozoön, of man is a minute cell 0.055 mm. long, specialized for active movement. Because of their motility, spermatozoa when first discovered were regarded as parasites living in the seminal fluid. The sperm cell is composed of a flattened *head*, short *neck*, and thread-like *tail* (Figs. 1 and 7).

The *head* is about 0.005 mm. in length. It appears oval in surface view, pear-shaped in profile. When stained, the anterior two-thirds of the head may be seen to form a *cap*, and the sharp border of this cap is the

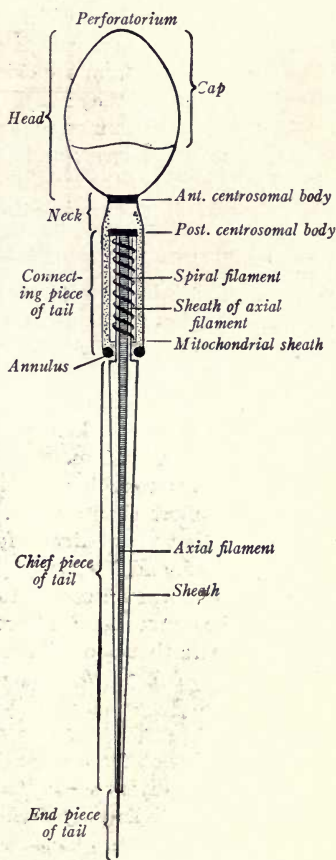


FIG. 7.—Diagram of a human spermatozoön, surface view (Meves, Bonnet).

perforatorium by means of which the spermatozoön penetrates the ovum. The head contains the nuclear elements of the sperm cell. The disc-shaped *neck* includes the *anterior centrosomal body*. The *tail* begins with the *posterior centrosomal body* and is divided into a short *connecting piece*, a *chief piece*, or *flagellum*, which forms about four-fifths of the length of the sperm cell, and a short *end piece*, or *terminal filament*. The connecting piece is marked off from the chief piece by the *annulus*. The connecting piece is traversed by the *axial filament* (*filum principale*), and is surrounded: (1) by the sheath common to it and to the flagellum; (2) by a sheath containing a *spiral filament*; and (3) by a *mitochondrial sheath*. The chief piece is composed of the *axial filament* surrounded by a *cytoplasmic sheath*, while the end piece comprises the naked continuation of the axial filament.

The spermatozoa are motile, being propelled by the movements of the tail. They swim always against a current at the rate of about 2.5 mm. a minute. This is important, as the outwardly directed currents induced by the ciliary action of the uterine tubes and uterus direct the spermatozoa by the shortest route to the infundibulum. Keibel has found spermatozoa alive three days after the execution of the criminal from whom they were obtained. They have been found motile in the uterine tube three and one-half weeks after coitus and have been kept alive eight days outside the body by artificial means. It is not known for how long a period spermatozoa are capable of fertilizing ova. Keibel holds that this would certainly be more than a week. However, Lillie (1915) has shown with sea urchins that the ability to fertilize is lost long before vitality or motility is impaired, and Mall (1918) concludes that the duration of the fertilizing power of human spermatozoa is safely less than the corresponding period in the ovum which is "probably for fully 24 hours after ovulation." Lode estimates that 200 million spermatozoa are liberated at an average ejaculation.

MITOSIS AND AMITOSIS

All cells arise from pre-existing cells by division. There are two methods of cell division—amitosis and mitosis.

Amitosis.—Cells may divide directly by the simple fission of their nuclei and cytoplasm. This rather infrequent process is called *amitosis*. Amitosis is said by many to occur only in moribund cells. It is the type of cell division demonstrable in the epithelium of the bladder.

Mitosis.—In the reproduction of typically active somatic cells and in all germ cells, complicated changes take place in the nucleus. These changes give rise to thread-like structures, hence the process is termed *mitosis* (thread) in distinction to amitosis (no thread). Mitosis is divided for convenience into four phases (Fig. 8).

Prophase.—1. The centrosome divides and the two minute bodies resulting from the division move apart, ultimately occupying positions at opposite poles of the nucleus (I–III).

2. Astral rays appear in the cytoplasm about each centriole. They radiate from it, and the threads of the central or achromatic spindle are formed between the two asters, thus constituting the *amphiaster* (II).

3. The nuclear membrane and nucleolus disappear, the karyoplasm and cytoplasm becoming confluent.

4. During the above changes the chromatic network of the resting nucleus resolves itself into a skein, or *spireme*, which soon shortens and breaks up into distinct, heavily-staining bodies, the *chromosomes* (II, III). A definite number of chromosomes is always found in the cells of a given species. The chromosomes may be block-shaped, rod-shaped, or bent in the form of a U or V.

5. The chromosomes arrange themselves in the equatorial plane of the central spindle (IV). If U- or V-shaped, the angle of each is directed toward a common center. The *amphiaster* and the *chromosomes* together constitute a *mitotic figure*, and at the end of the prophase this is called a *monaster*.

Metaphase.—The longitudinal splitting of the chromosomes into exactly similar halves constitutes the *metaphase* (IV, V). The aim of mitosis is thus accomplished, an accurate division of the chromatin between the nuclei of the daughter cells.

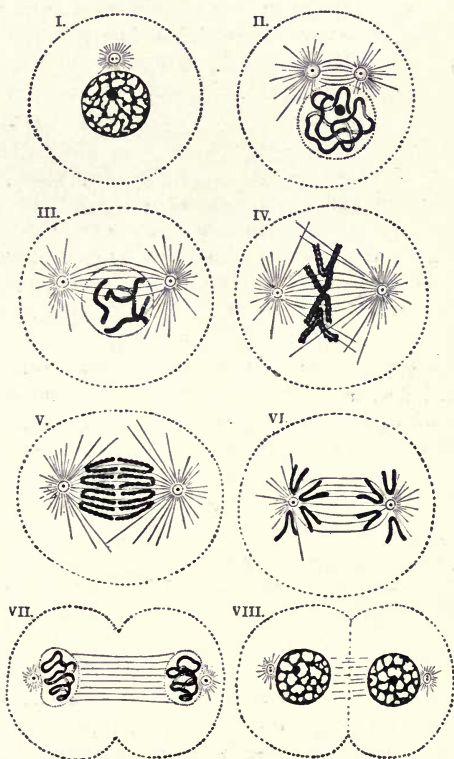


FIG. 8.—Diagrams of the phases of mitosis (Schäfer).

Anaphase.—At this stage the two groups of daughter chromosomes separate and move up along the central spindle fibers, each toward one of the two asters. Hence this is called the *diaster* stage (V, VI). At this stage, the centrioles may each divide in preparation for the next division of the daughter cells.

Telophase.—1. The daughter chromosomes resolve themselves into a reticulum and daughter nuclei are formed (VII, VIII).

2. The cytoplasm divides in a plane perpendicular to the axis of the mitotic spindle (VIII). Two complete daughter cells have thus arisen from the mother cell.

The number of chromosomes is constant in the cells of a given species. The smallest number of chromosomes, two, occurs in *Ascaris megalocephala univalens*, a round worm parasitic in the intestine of the horse. The largest number known is found in the brine shrimp, *Artemia*, where 168 have been counted.

The number for the human cell is in doubt. Guyer (1910) and Montgomery (1912) counted 22 in the spermatogonia of negroes. For white spermatogonia, Guyer (1913) reported considerably larger numbers (count not given) than he had formerly found in the negro. This is suggestive in view of Winiwarter's (1912) apparently careful work on whites which gave for the oöcyte 48, for the spermatogone 47; although this enumeration needs confirmation, it has been tentatively accepted by many. Wieman (1913) found the most frequent number in various white somatic cells to be 34, but recently (1917) he asserts that the number in both negro and white spermatogonia is 24, thereby agreeing with Duesberg's (1906) count.

MATURATION

We have seen that reproduction in vertebrates follows upon the union of male and female germ cells. Without special provision this union would necessarily double the number of chromosomes at each generation. Such progressive increase is prevented by the processes of *maturation* which take place in both the ovum and spermatozoön.

Maturation may be defined as a process of cell division during which the number of chromosomes in the germ cells is reduced to one-half the number characteristic for the species. Its significance in the mechanism of inheritance is discussed on p. 22.

Spermatogenesis.—The spermatozoa take their origin in the germinal epithelium of the testis. Their general development, or *spermatogenesis*, may be studied in the testis of man or of the rat; the details of their maturation stages in *Ascaris* or in insects. Two types of cells are recognized in the germinal epithelium of the seminiferous tubules: the *sustentacular cells* (of Sertoli), and the male germ cells or *spermatogonia* (Fig. 9). The spermatogonia divide, one daughter cell forming what is known as a *primary spermatocyte*. The other daughter cell persists as a spermatogone, and, by continued division during the sexual life of the individual,

gives rise to other primary spermatocytes. The primary spermatocytes correspond to the ova before maturation. Each contains the number of chromosomes typical for the male of the species.

The process of maturation consists in two cell divisions of the primary spermatocytes, each producing, first, two *secondary spermatocytes*, and these in turn four cells known as *spermatids*. During these cell divisions the number of chromosomes is reduced to half the original number in the spermatogonia. Each spermatid now becomes transformed into a mature spermatozoön (Fig. 10). The nucleus forms the larger part of the head; the centrosome divides, the resulting moieties passing to the extremities of the neck. The posterior centrosome is prolonged to

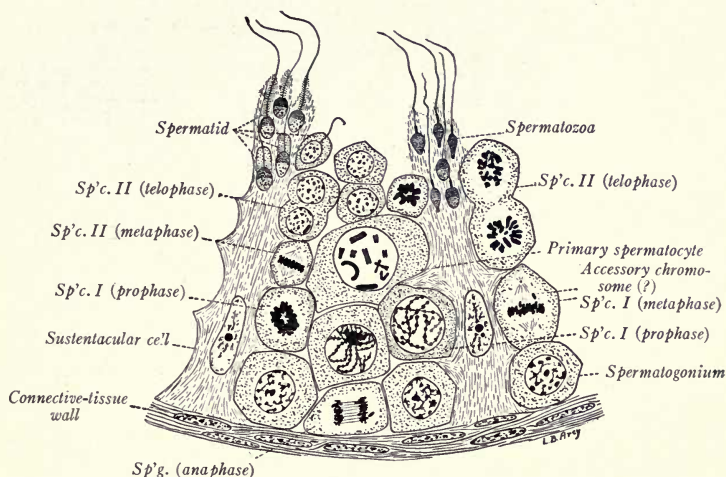


FIG. 9.—Stages in the spermatogenesis of man arranged in a composite to represent a portion of a seminiferous tubule sectioned transversely. $\times 900$.

become the axial filament, and the cytoplasm forms the sheaths of the neck and tail. The spiral filament of the connecting piece is derived from the cytoplasmic mitochondria.

The way in which the number of chromosomes is reduced may be seen in the spermatogenesis of *Ascaris* (Fig. 11). Four chromosomes are typical for *Ascaris megalocephala bivalens* and each spermatogone contains this number. In the early prophase of the primary spermatocyte there appears a spireme thread consisting of four parallel rows of granules (*B*). This thread breaks in two and forms two quadruple structures known as *tetrads* (*D-F*); each is equivalent to two original chromosomes, paired side

by side and split lengthwise to make a bundle of four. At the metaphase (*G*) each *tetrad* divides into its two original chromosomes which already show evidence of longitudinal fission and are termed *dyads*. One pair of dyads goes to each of the daughter cells, or secondary spermatocytes (*G-I*). Without the formation of a nuclear membrane, the second maturation spindle appears at once, the two dyads split into four *monads*, and each daughter spermatid receives two single chromosomes (monads), or one-half the number characteristic for the species. The tetrad, therefore, repre-

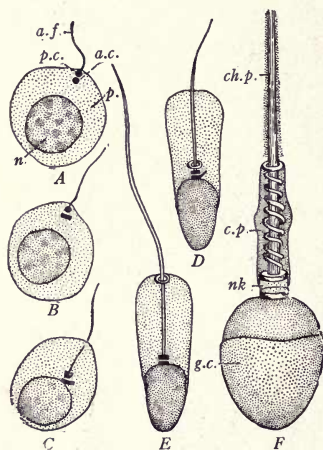


FIG. 10.—Diagrams of the development of spermatozoa (after Meves in Lewis and Stöhr). *a.c.*, Anterior centrosome; *a.f.*, axial filament; *c.p.*, connecting piece; *ch.p.*, chief piece; *g.c.*, cap; *n.*, nucleus; *nk.*, neck; *p.*, protoplasm; *p.c.*, posterior centrosome.

sents a precocious division of the chromosomes in preparation for two rapidly succeeding cell divisions which occur without the intervention of the customary resting periods. The easily understood tetrads are not formed in most animals, although the outcome of maturation is identical in either case. A diagram of maturation is shown in Fig. 12. The first maturation division in *Ascaris* is probably *reductional*, each daughter nucleus receiving two complete chromosomes of the original four, whereas in the second maturation division, as in ordinary mitosis, each daughter nucleus receives a half of each of the two chromosomes, these being split lengthwise. In the latter case the division is *equational*, each daughter nucleus receiving chromosomes bearing similar hereditary qualities.

In some animals the sequence of events is reversed, reduction occurring at the second maturation division. In many insects and some vertebrates

it has been shown that the number of chromosomes in the oögonia is even, the number in the spermatogonia odd. An exact halving of the spermatogonial number of chromosomes can not occur in such cases (p. 23).

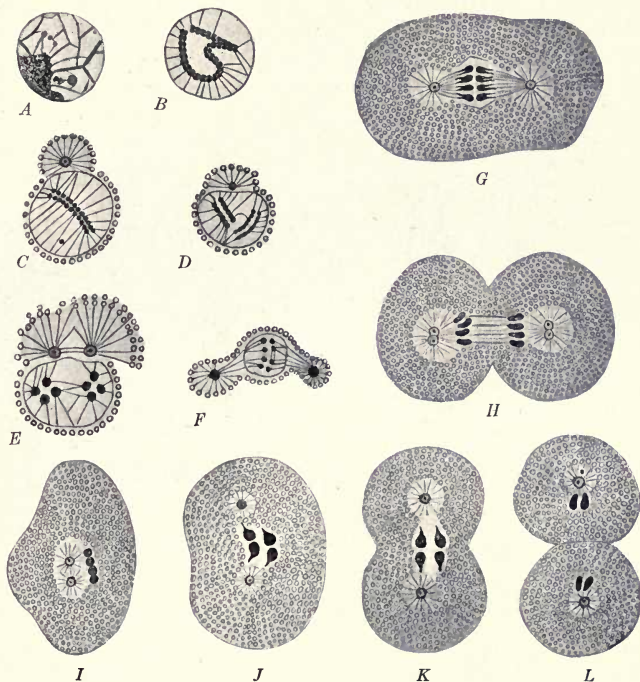


FIG. 11.—Reduction of chromosomes in the spermatogenesis of *Ascaris megalocephala bivalens* (Brauer, Wilson). \times about 1100. A–G, successive stages in the division of the primary spermatocyte. The original reticulum undergoes a very early division of the chromatin granules which then form a quadruply split spireme (B, in profile). This becomes shorter (C, in profile), and then breaks in two to form two tetrads (D, in profile), (E, on end). F, G, H, first division to form two secondary spermatocytes, each receiving two dyads. I, secondary spermatocyte. J, K, the same dividing. L, two resulting spermatids, each containing two monads or chromosomes.

Oögenesis.—During oögenesis, the ova undergo a similar process of maturation. Two cell divisions take place, but with this difference: the cleavage is *unequal*, and, instead of four cells of equal size resulting, there are formed one large ripe ovum, or *oöcyte*, and three rudimentary or abortive ova known as *polar bodies*, or *polocytes*. The number of chromosomes

is reduced in the same manner as in the spermatocyte, so that the ripe ovum and each polar cell contain one-half the number of chromosomes found in the immature ovum or primary oöcyte.

The primitive female germ cells, from which new ova are produced by cell division, are called *oögonia* and their daughter cells after a period of growth within the ovary are the *primary oöcytes*, comparable to the primary spermatocytes of the male (Fig. 12). During maturation the ovum and first polocyte are termed *secondary oöcytes* (comparable to secondary spermatocytes); the mature ovum and second polocyte, with

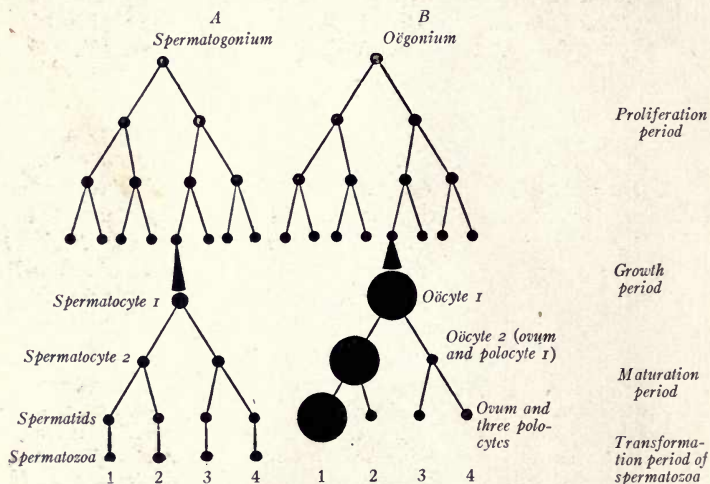


FIG. 12.—Diagrams of maturation in spermatogenesis and oögenesis (Boveri).

the daughter cells of the first polocyte, are comparable to the spermatids. Each spermatid, however, may form a mature spermatozoön, but only one of the four daughter cells of the primary oöcyte becomes a mature ovum. The ovum develops at the expense of the three polocytes which are abortive and degenerate eventually, though it has been shown that in the ova of some insects the polar cell may be fertilized and segment several times like a normal ovum. In most animals, the actual division of the first polocyte into two daughter cells is suppressed. The nucleus of the ovum after maturation is known as the *female pronucleus*.

Maturation of the Mouse Ovum.—Typical maturation stages may be studied in the easily obtained ova of the mouse (Long and Mark, Carnegie Inst. Publ. No. 142). The first polocyte is formed while the ovum is

still in the Graafian follicle. In the formation of the maturation spindle, no astral rays and no typical centrosomes have been observed. The chromosomes are V-shaped. The first polar cell is constricted from the ovum and lies beneath the zona pellucida as a spherical mass about 25 micra in diameter (Fig. 13). Both ovum and polar cell (secondary

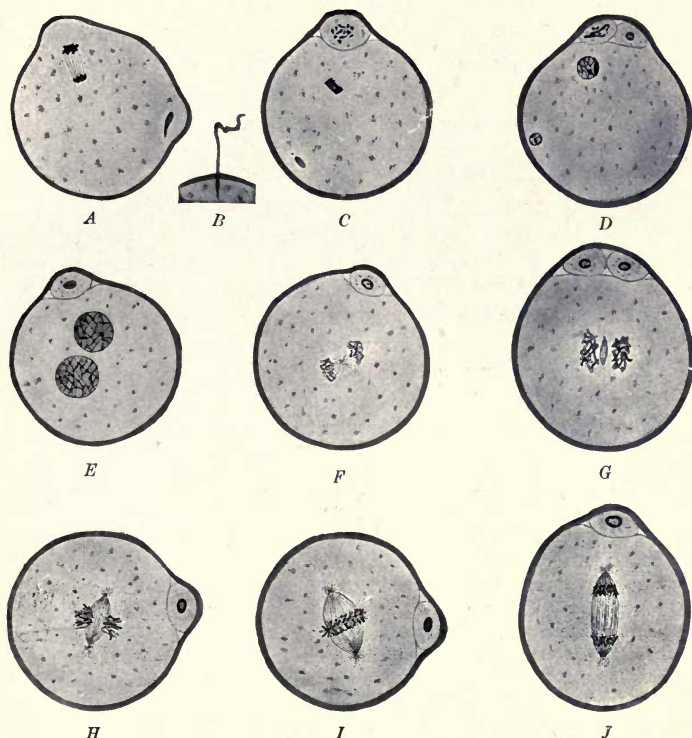


FIG. 13.—Maturation and fertilization of the ovum of the mouse (after Sobotta). *A*, *C*–*J*, $\times 500$; *B* $\times 750$. *A*–*D*, entrance of the spermatozoön and formation of the polar cells. *D*–*E*, development of the pronuclei. *F*–*J*, successive stage in the first division of the fertilized ovum.

oöcytes) contain 20 chromosomes, or half the number normal for the mouse. The first maturation division is the reductional one and the chromosomes take the form of tetrads.

After ovulation has taken place, the ovum lies in the ampulla of the uterine tube. If fertilization occurs, a second polocyte is cut off, the nucleus of the ovum forming no membrane between the production of

the first and second polar bodies (Fig. 13 A-D). The second maturation spindle and second polar cell are smaller than the first. Immediately after the formation of the second polar cell, the chromosomes resolve themselves into a reticulum and the *female pronucleus* is formed (Fig. 13 D).

Maturation of the Human Ovum.—The only observations are those of Thompson (1919), who believes to have identified stages in the formation of all three polar cells prior to ovulation or fertilization. The evidence presented, however, can hardly be accepted as conclusive.

FERTILIZATION

The stimulus initiating development in most multicellular animals is furnished by a spermatozoön which penetrates the ovum and fuses with its nucleus. These events constitute *fertilization*.

Only motile spermatozoa are able to attach to the surface of an egg; it is probable that forces allied to phagocytosis, rather than vibrational energy, accomplish the actual 'penetration.' Spermatozoa may enter the mammalian ovum at any point. If fertilization is delayed too long after ovulation, the ovum may be weakened and allow the entrance of several spermatozoa. This is known as *polyspermy*. In such cases, however, only one spermatozoön unites with the female pronucleus.

The fundamental results of the process of fertilization are: (1) the *union of the male and female chromosomes* to form the *cleavage nucleus* of the fertilized ovum; (2) the *initiation of cell division*, or cleavage of the ovum.

These two factors are separate and independent phenomena. It has been shown by Boveri and others that fragments of sea urchin's ova containing no part of the nucleus may be fertilized by spermatozoa, segment, and develop into larvæ. The female chromosomes are thus not essential to the process of segmentation. Loeb, on the other hand, has shown that the ova of invertebrates may be made to develop by chemical and mechanical means without the coöperation of the spermatozoön (*artificial parthenogenesis*). Even adult frogs have been reared from mechanically stimulated eggs. It is well known that the ova of certain invertebrates develop normally without fertilization, that is, parthenogenetically. These facts show that the union of the male and female pronuclei is not the means of initiating the development of the ova. In all vertebrates it is, nevertheless, the end and aim of fertilization.

Lillie (1912; 1913) has recently shown that the cortex of sea urchin's ova produces a substance which he terms *fertilizin*. This substance he regards as an amboceptor essential to fertilization, with one side chain which agglutinates and attracts the spermatozoa, and another side chain which activates the cytoplasm and initiates the cleavage of the ovum. According to Loeb (1916), agglutination is proved in but few forms and Lillie's interpretation fails to meet all the facts. Loeb (1913) holds that the spermatozoön actually activates the ovum to develop by increasing its oxidations and by rendering it immune to the toxic effects of oxidation.

Fertilization of the Mouse Ovum.—Normally, a single spermatozoön enters the ovum six to ten hours after coitus. While the second polar cell is forming, the spermatozoön penetrates the ovum and loses its tail. Its

head enlarges and is converted into the *male pronucleus* (Fig. 13 D). The pronuclei, male and female, approach each other and resolve themselves first into a spireme stage, then into two groups of 20 chromosomes. A centrosome, possibly that of the male cell, appears between them, divides into two, and soon the first cleavage spindle is formed (F-H). The 20 male and 20 female chromosomes arrange themselves in the equatorial plane of the spindle, thus making the original number of 40 (I). Fertilization is now complete and the ovum divides in the ordinary way, the daughter cells each receiving equal numbers of maternal and paternal chromosomes.

Fertilization of the Human Ovum.—Spermatozoa, deposited in the vagina at coitus, ascend through the uterus and uterine tubes, their course being directed by the downward stroking cilia (p. 12). They probably reach the ampulla of the uterine tube two or more hours after coitus. Here the penetration of the ovum is believed usually to take place about one day after coitus (Mall, 1918, cf. p. 12) although it has never been observed. This conclusion is supported by direct observation on other mammals and by the frequency of tubal pregnancies at this site. Normally, then, the embryo begins its development in the uterine tube, thence passes to the uterus and becomes embedded in the uterine mucosa. Rarely ova may be fertilized and start developing before they enter the tube, but fertilization within the uterus is usually denied.

Twin Development.—Usually but one human ovum is produced and fertilized at coitus. The development of two or more embryos within the uterus is commonly due to the ripening, expulsion, and subsequent fertilization of an equal number of ova. In such cases *ordinary*, or *fraternal twins*, triplets, and so on, of the same or opposite sex, result. *Identical*, or *duplicate twins*, that is, those always of the same sex and strikingly similar in form and feature, are believed to arise from the fission of the embryonic cell mass, each portion then developing as a separate embryo within the common chorion. The identical quadruplets of certain armadillos are known to result from the division of a single blastoderm into four parts. Separate development of the cleavage cells can also be produced experimentally in many of the lower animals.

Double Monsters.—Occasionally twins are conjoined. All degrees of union, from almost complete separation to fusion throughout the entire body-length, are known. If there is considerable disparity in size, the smaller is termed the parasite; in such cases the extent of attachment and dependency grades down to included twin (fetus in fetu) and tumor-like fetal inclusions. In some asymmetrical monsters the duplication is partial, as doubling of the head or legs. All of these terata, like identical twins, are regarded as the products of a single ovum, but with variably incomplete fission, or bifurcation, of the embryonic mass.

Superfetation.—An ovum, liberated by a pregnant woman and fertilized at a later coitus, may develop into a second, younger fetus. This rare condition, often denied, is called *superfetation* and is not to be confused with strikingly unequal twin development. Until the fourth month of pregnancy superfetation is theoretically possible (p. 237).

The Significance of Mitosis, Maturation and Fertilization.—The complicated processes of mitosis serve the purpose of accurately dividing the chromatic substance of the nucleus in such a way that the self-perpetuating chromosomes of each daughter cell may be the same both quantitatively and qualitatively. This is of importance since it is believed by most students of heredity that chromatin particles, or *genes*, in the chromosomes bear the hereditary characters, and that these are arranged in definite linear order in particular chromosomes. At maturation there is a side by side union of like chromosomes, one member of each pair having come from the father, the other from the mother of the preceding generation; each member, however, carries the same general set of hereditary characters as its mate. At this stage of chromosomal conjugation there may be an interchange, or 'crossing over,' of corresponding genes, resulting in new hereditary combinations. The reducing division of maturation separates whole chromosomes of each pair, but chance alone governs the actual assortment of paternal and maternal members to the daughter cells; this mitosis obviously halves the chromosome number characteristic for the species. The significance of the equational maturation mitosis, beyond accomplishing mere cellular multiplication, is obscure.

Fertilization initiates development and restores the original number of chromosome pairs (cf. p. 20). The fertilized ovum derives its nuclear substance equally from both parents, the cytoplasm and yolk almost entirely from the mother, the centrosome probably from the father.

Mendel's Law of Heredity.—Experiments show that most hereditary characters fall into two opposing groups, the contrasted pairs of which are termed *allelomorphs*. As an example, we may take the hereditary tendencies for black and blue eyes. It is believed that there are paired chromatic particles, or *genes*, which are responsible for these hereditary tendencies, and that paired spermatogonial chromosomes bear one each of these genes. Each chromosome pair in separate germ cells may possess similar genes, both bearing black-eyed tendencies or both blue-eyed tendencies, or opposing genes, bearing the one black, the other blue-eyed tendencies. It is assumed that at maturation these paired genes are separated along with the chromosomes, and that one only of each pair is retained in each germ cell.

In our example, either a blue-eyed or a black-eyed tendency-bearing particle would be retained. At fertilization the segregated genes of one sex may enter into new combinations with those from the other sex. Three combinations are possible. If the color of the eyes be taken as the hereditary character: (1) two 'black' germ cells may unite; (2) two 'blue' germ cells may unite; (3) a 'black' germ cell may unite with a 'blue' germ cell. The offspring in (1) will all have black eyes, and, if interbred, their progeny will likewise inherit black eyes exclusively. Similarly, the offspring in (2), and if these are interbred their progeny as well, will include nothing but blue-eyed individuals. The first generation from the cross in (3) will have black eyes solely, for black in the present example is *dominant*, as it is termed. Such black-eyed individuals, nevertheless, possess both black- and blue-eyed bearing genes their germ in cells; in the progeny resulting from the interbreeding of this class the original condition is repeated—pure blacks, impure blacks which hold blue *recessive*, and pure blues will be formed in the ratio of 1:3:1 respectively. It is thus seen that blue-eyed children may be born of black-eyed parents, whereas blue-eyed parents can never have black-eyed offspring. Many such *allelomorphic* pairs of hereditary characters are known.

Cytoplasmic Inheritance.—Certain eggs show distinct cytoplasmic zones which cleavage later segregates into groups of cells destined to form definite organs or parts. In a sense this represents a refined sort of preformation, but prelocalization is a more exact

term. From these facts Conklin and Loeb argue that the cytoplasm is really the embryo in the rough, the nucleus, through Mendelian heredity, adding only the finer details. Morgan, among others, refuses to admit the validity of this interpretation.

The Determination of Sex.—The assumption that the chromosomes are the carriers of hereditary tendencies is borne out by experimental breeding (Morgan) and by the correlated observations of cytologists on the germ cells of invertebrates, especially insects, and of some vertebrates. According to Winiwarter (Arch. de Biol., T. 27, 1912) the nuclei of human spermatogonia contain 47 chromosomes, while those of the oögonia contain 48. When the reduction of chromosomes takes place in the male cells, one unpaired chromosome fails to divide and passes intact to one or the other daughter cells; hence half of the spermatids contain 24 chromosomes, the other half only 23. All the oöcytes and polocytes, on the contrary, contain 24. There is thus one extra chromosome in each mature ovum and in each of half the spermatozoa. This chromosome, because of peculiarities of size or shape, can be identified easily in many animals, and is termed the *accessory X*, or *sex chromosome*. McClung was the first to assume that the X chromosome is a sex determinant. It has since been shown by Wilson and others that the sex chromosome carries the female sexual characters. When, in the case under consideration, a spermatozoön with 24 chromosomes fertilizes an ovum, the resulting embryo is a female, its somatic nuclei containing 48 chromosomes. An ovum fertilized by a sperm cell containing only 23 chromosomes (without the sex chromosome) produces a male with somatic nuclei containing but 47 chromosomes. These observations of Winiwarter on man have not yet been confirmed by other investigators. There is no reason to doubt, however, that sex is determined in man essentially in the manner described, which agrees with the easily observed phenomena in insects.

In certain moths and birds the sex chromosome system is the exact reverse of the common scheme just explained, but the operation of the mechanism is otherwise similar. The spermatozoa of these forms are all alike in chromosome constitution while the eggs are of two sorts.

CHAPTER II

CLEAVAGE OF THE FERTILIZED OVUM AND THE ORIGIN OF THE GERM LAYERS

CLEAVAGE

THE processes of cleavage, or segmentation, not having been observed in human ova, must be studied in other vertebrates. It is probable that the early development of all vertebrates is, in its essentials, the same. Cleavage may be modified, however, by the presence in the ovum of large quantities of nutritive yolk. In many vertebrate ova the yolk collects at one end, termed the *vegetal pole*, in contrast to the more purely protoplasmic *animal pole*. Such ova are said to be *telolecithal*. Examples are the ova of fishes, amphibians, reptiles, and birds. When very little yolk is present, the ovum is said to be *isolecithal*. Examples are the ova of *Amphioxus*, the higher mammals, and man. The typical processes of cleavage may be studied most easily in the fertilized ova of invertebrates (Echinoderms, Annelids, and Mollusks). Among Chordates, the early processes in development are primitive in a fish-like form, *Amphioxus*. The yolk modifies the development of the amphibian and bird egg, while the early structure of the mammalian embryo can be explained only by assuming that the ova of the higher Mammalia at one time contained a considerable amount of yolk, like the ovum of the bird and of the lowest mammals, and the influence of this condition persists.

Cleavage in *Amphioxus*.—The ovum is essentially isolecithal, since it contains but little yolk (Fig. 14). About one hour after fertilization it divides vertically into two nearly equal daughter cells, or *blastomeres*. The process is known as cell *cleavage*, or *segmentation*, and takes place by mitosis. Within the next hour the daughter cells again cleave in the vertical plane, at right angles to the first division, thus forming four cells. Fifteen minutes later a third division takes place in a horizontal plane. As the yolk is somewhat more abundant at the vegetal pole of the four cells, the mitotic spindles lie nearer the animal pole. Consequently, in the eight-celled stage the upper tier of four cells is smaller than the lower four. By successive cleavages, first in the vertical, then in the horizontal plane a 16- and 32-celled embryo is formed. The upper two tiers are now smaller, and a cavity, the *blastocœle*, is enclosed by the cells. The embryo at this stage is sometimes called a *morula* because of its resemblance to a

mulberry. In subsequent cleavages, as development proceeds, the size of the cells is diminished while the cavity enlarges (Fig. 14). The embryo

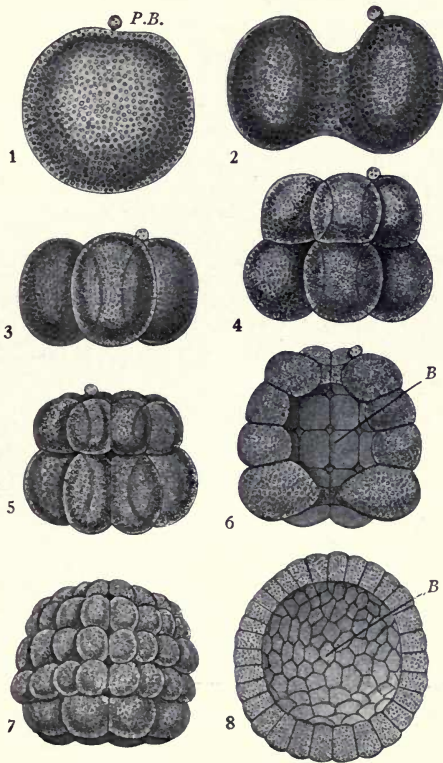


FIG. 14.—Cleavage of the egg of *Amphioxus* (after Hatschek). $\times 200$. 1. The egg before the commencement of development; only one polar body, *P.B.*, is present, the other having been lost during ovulation. 2. The ovum in the act of dividing, by a vertical cleft, into two equal blastomeres. 3. Stage with four equal blastomeres. 4. Stage with eight blastomeres; an upper tier of four slightly smaller ones and a lower tier of four slightly larger ones. 5. Stage with sixteen blastomeres in two tiers, each of eight. 6. Stage with thirty-two blastomeres, in four tiers, each of eight; the embryo is represented bisected to show the cleavage cavity or blastocœle, *B*. 7. Later stage; the blastomeres have increased in number by further division. 8. Blastula stage bisected to show the blastocœle, *B*.

is now a *blastula*, nearly spherical in form and about four hours old. The cleavage of the *Amphioxus* ovum is thus *holoblastic*, that is, *complete*, and nearly *equal*.

Cleavage in Amphibia.—These ova contain so much yolk that the nucleus and most of the cytoplasm lie at the upper, or animal pole. The first cleavage spindle appears eccentrically in this cytoplasm. The first two cleavage planes are vertical and at right angles, and the four resulting cells are nearly equal. The spindles for the third cleavage are located near the animal pole, and the cleavage takes place in a horizontal plane. As a result, the upper four cells are much smaller than the lower four (Fig. 15 A). The large, yolk-laden cells divide more slowly than the upper, small cells (B-D). At the blastula stage, the cavity is small, and the cells of the vegetal pole are each many times larger than those at the animal pole (E,F). The cleavage of the frog's ovum is thus *complete* but *unequal*.

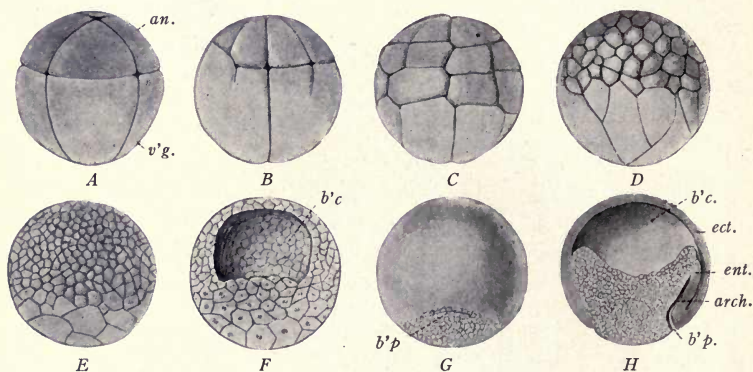


FIG. 15.—Cleavage and gastrulation in the frog. $\times 12$. A-D, cleavage stages; E, blastula; F, blastula in median section; G, early gastrula; H, median section of stage G. *an.*, Animal cells; *arch.*, archenteron; *b'c.*, blastocoele; *b'p.*, blastopore; *ect.*, ectoderm; *ent.*, entoderm; *v'g.*, vegetal cells.

Cleavage in Reptiles and Birds.—The ova of these vertebrates contain a large amount of yolk. There is very little pure cytoplasm except at the animal pole, and here the nucleus is located (Fig. 3). When segmentation begins, the first cleavage plane is vertical but the inert yolk does not cleave. The segmentation is thus *meroblastic*, or *incomplete*. In the hen's ovum, the cytoplasm is divided by successive vertical furrows into a mosaic of cells, which, as it increases in size, forms a cap-like structure upon the surface of the yolk (Fig. 16 A). These cells are separated from the yolk beneath by horizontal cleavage furrows, and successive horizontal cleavages give rise to several layers of cells (Fig. 16 B). The space between cells and yolk mass may be compared to the blastula cavity of *Amphioxus* and the frog (Fig. 18). The cellular cap is termed the *germinal disc*, or *blastoderm*. The yolk mass, which forms the floor of the blastula cavity

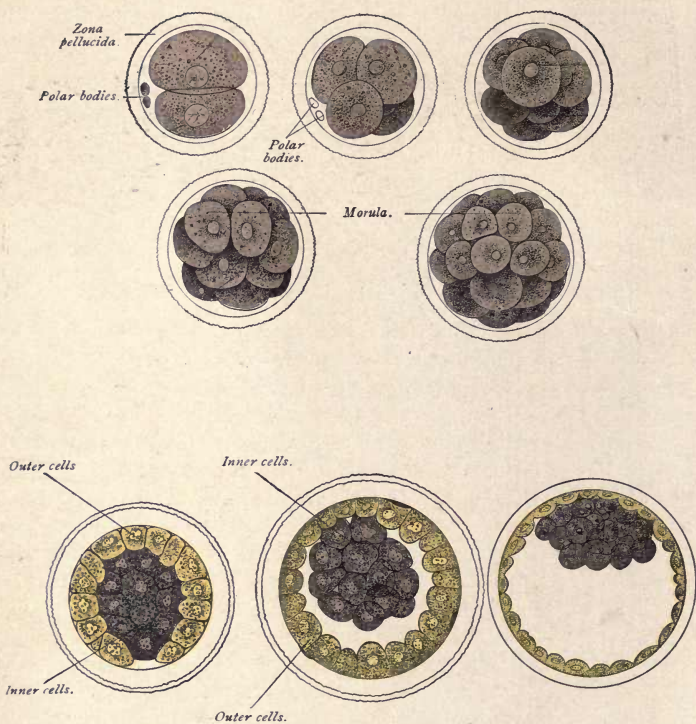


FIG. 17.—Diagrams showing the cleavage of the mammalian (rabbit's) ovum and the formation of the blastodermic vesicle (Allen Thomson, after van Beneden). $\times 200$.

and the greater part of the ovum, may be compared to the large, yolk-laden cells at the vegetal pole of the frog's blastula. The yolk mass never divides but is gradually used up in supplying nutriment to the embryo which is developed from the cells of the germinal disc. At the periphery of the blastoderm new cells constantly form until they enclose the yolk (Fig. 18 C).

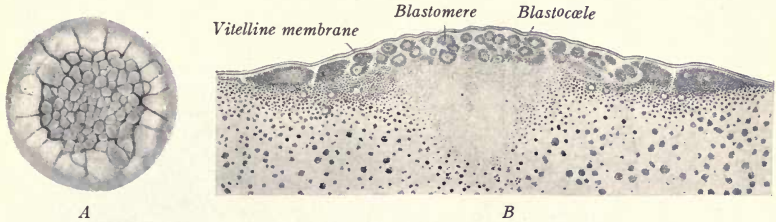


FIG. 16.—Cleavage of the pigeon's ovum (after Blount). A, blastoderm in surface view; B, in vertical section.

Cleavage in Mammals.—The ovum of all the higher mammals, like that of man, is isolecithal and nearly microscopic in size. Its cleavage has been studied in several mammals but the rabbit's ovum will serve as an example. The cleavage is complete and nearly equal (Fig. 17), a cluster of approximately uniform cells being formed within the zona pellucida. This corresponds to the morula stage of *Amphioxus*. Next an *inner mass of cells* is formed that is equivalent to the *germinal disc*, or *blastoderm*, of the chick embryo (Fig. 17). The inner cell mass is overgrown by an outer layer which is termed the *trophoblast*, because, in mammals, it later supplies nutriment to the embryo from the uterine wall. Fluid next appears between the outer layer and the inner cell mass, thereby separating the two except at the animal pole. As the fluid increases in amount, a hollow vesicle results, its walls composed of the single-layered trophoblast except where this is in contact with the inner cell mass. This stage is known as that of the *blastodermic vesicle*. It is usually spherical or ovoid in form, as in the rabbit, and probably this is the form of the human ovum at this stage. In the rabbit the vesicle is 4.5 mm. long before it becomes embedded in the wall of the uterus. Among Ungulates (hoofed animals), the vesicle is greatly elongated and attains a length of several centimeters, as in the pig.

If we compare the mammalian blastodermic vesicle with the blastula stages of *Amphioxus*, the frog, and the bird, it will be seen that it is to be homologized with the bird's blastula, not with that of *Amphioxus* (Fig. 18). In each case there is an inner cell mass of the germinal disc. The tro-

phectoderm of the mammal represents a precocious development of cells, which, in the bird, later envelop the yolk. The cavity of the vesicle is to be compared, not with the blastula cavity of *Amphioxus* and the frog, but with the *yolk mass plus the cleft-like blastocæle of the bird's ovum*. The mammalian ovum, although almost devoid of yolk, thus develops much

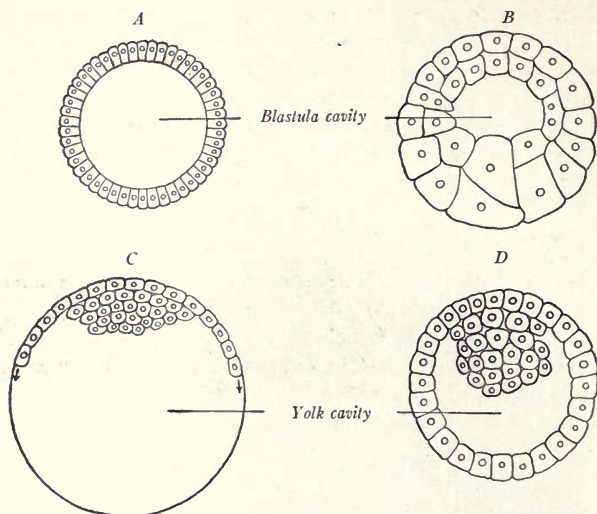


FIG. 18.—Diagrams showing the blastula: *A*, of *Amphioxus*; *B*, of frog; *C*, of chick; *D*, blastodermic vesicle of mammal.

like the yolk-laden ova of reptiles and birds. This similarity has an evolutionary significance. Its cleavage, however, is complete and the early stages in its development are abbreviated.

In Primates, but one cleavage stage has been observed. This, a four-celled ovum of *Macacus nemestrinus* figured by Selenka, shows the cells nearly equal, and oval in form. This ovum was found in the uterine tube of the monkey and shows that, in Primates and probably in man, cleavage as in other mammals take place normally in the oviducts.

THE FORMATION OF ECTODERM AND ENTODERM (GASTRULATION)

The blastula and early blastodermic vesicle show no differentiation into layers. Such differentiation takes place later in all vertebrate embryos, giving rise first to the *ectoderm* and *entoderm*, and finally to the *mesoderm*. From these three *primary germ layers* all tissues and organs of the body are derived.

The processes of *gastrulation*, by which ectoderm and entoderm arise, and of mesoderm formation will be treated separately.

Amphioxus and Amphibia.—In these animals the larger cells at the vegetal pole of the blastula either fold inward, that is, invaginate (Amphioxus, Fig. 19), or are for the most part asymmetrically overgrown by the more rapidly dividing cells of the animal pole (amphibia, Fig. 15 *G, H*). Eventually the invaginating cells obliterate the blastula cavity and come in contact with the outer layer of cells (Fig. 19). The new cavity thus formed is the primitive gut, or *archenteron*, and its narrowed mouth is the *blastopore*. The outer layer of cells is the *ectoderm*, the inner, newly formed layer is the *entoderm*. The entodermal cells are henceforth concerned in the nutrition and metabolism of the body. The embryo is now termed a *Gastrula* (little stomach).

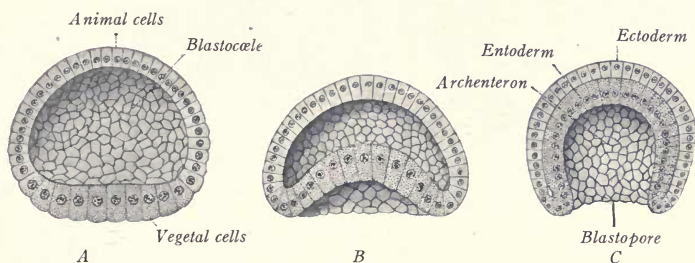


FIG. 19.—Gastrulation in *Amphioxus*. \times about 200. *A*, blastula; *B, C*, early and late gastrulæ.

Reptiles and Birds.—The germinal disc, or blastoderm, in these animals lies like a cap on the surface of inert yolk (Fig. 3). Since the enormous amount of yolk makes gastrulation as in *Amphioxus* and amphibians impossible, the process exhibits marked modifications.

There appears caudally on the blastoderm of reptiles a pit-like depression. From this slight invagination a proliferation of cells forms a layer which spreads beneath the ectoderm. The inner layer, originating in this manner, is the *entoderm*, and the region of the pit, where ectoderm and entoderm are continuous, is the *blastopore*. In Fig. 21 *A* these changes are complete.

In birds, the caudal portion of the blastoderm is rolled or tucked under, the inner layer formed in this way constituting the *entoderm*. The marginal region where ectoderm and entoderm meet bounds the *blastopore*, while the space between entoderm and yolk is the *archenteron*.

Mammals.—As in cleavage, so also in gastrulation the mammalian ovum exhibits a modified behavior indicative of an ancestral yolk-rich condition. Cells on the under surface of the inner cell mass become arranged in a definite sheet, the *entoderm*, which rapidly spreads and lines

the blastodermic vesicle (Figs. 17, 74 A and 75). The entodermal layer is usually said to arise by splitting, or delamination. Recent careful work, however, shows that in some mammals, at least, the entoderm cells originally lie within the inner cell mass and reach the inner surface by migration (Hartman, 1919).

ORIGIN OF THE MESODERM, NOTOCHORD AND NEURAL TUBE

Amphioxus and Amphibia.—The dorsal portion of the entodermal sheet, which forms the roof of the archenteron in *Amphioxus*, gives rise to paired lateral diverticula, or *cœlomic pouches* (Fig. 20). These separate both from the plate of cells in the mid-dorsal line (which forms the *noto-*

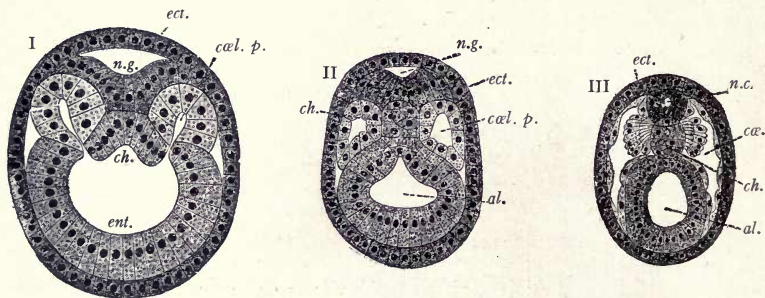


FIG. 20.—Origin of the mesoderm in *Amphioxus* (after Hatschek). \times about 425. n.g., Neural groove; n.c., neural canal; ch., anlage of notochord; cœl. p., cœlomic pouch; ect., ectoderm; ent., entoderm; al., cavity of gut; cœ., cœlom or body cavity.

chord), and from the entoderm of the gut, and become the *primary mesoderm*. The mesodermal pouches grow ventral and their cavities form the *cœlom*, or body cavity. Their outer walls, with the ectoderm, form the body wall, or *somatopleure*; their inner walls, with the gut entoderm, form the intestinal wall, or *splanchnopleure*. In the meantime, a dorsal plate of cells, cut off from the ectoderm, has formed the *neural tube* (anlage of the nervous system), and the notochordal plate has become a cord, or cylinder, of cells (axial skeleton) extending the length of the embryo. In this simple fashion the ground plan of the chordate body is developed.

In *Amphibia*, instead of mesodermal diverticula solid plates grow out from the dorsal entoderm between the ectoderm and entoderm. Later, these plates split into two layers and the cavity so formed give rise to the cœlom.

Reptiles.—The same pocket-like depression in the caudal portion of the blastoderm, that gave rise to the cells of the entodermal layer, now invaginates more extensively and forms a pouch which pushes forward

between ectoderm and entoderm (Fig. 21 A and B). The size of the invagination cavity varies in different species; in some it is elongated and narrow, being confined to the middle line of the blastoderm. The floor of

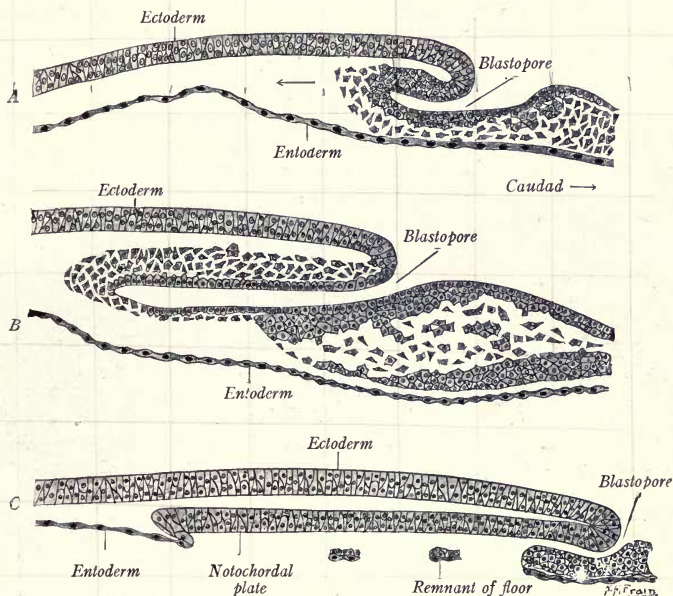


FIG. 21.—Longitudinal sections of the snake's blastoderm at various stages to show the origin of the notochordal plate (adapted after Hertwig).

this pouch soon fuses with the underlying entoderm and the two thin, rupture, and disappear, thus putting the cavity of the pouch temporarily in communication with the space (archenteron) beneath the entoderm

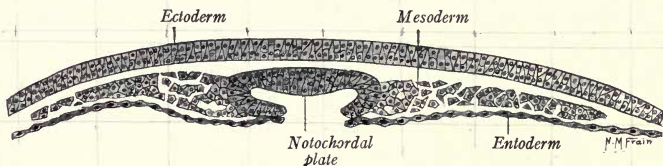


FIG. 22.—Transverse section of a snake's blastoderm at a level corresponding to the middle of Fig. 21 C (adapted after Hertwig).

(Fig. 21 C). The cells of the roof persist as the *notochordal plate*, which later gives rise to the notochord. The neural folds arise before the mouth of the pouch (blastopore) closes up, and, fusing to form the neural tube,

incorporate the blastopore into its floor. This temporary communication between the neural tube and the primitive enteric cavity is the *neurenteric canal* (cf. Fig. 21 C); it is found in all the vertebrate groups (cf. Fig. 78). A transverse section through the invaginated pouch, at the time of rupture of its floor, and the underlying entoderm will make clear the relatively slight lateral extent of these changes (Fig. 22).

From about the blastopore, and from the walls of the pouch, mesodermal plates arise and extend like wings between the ectoderm and entoderm (Fig. 22). As in amphibia, they later separate into outer (somatic) and inner (splanchnic) layers enclosing the coelom (cf. Fig. 29 B). The relation

between notochordal plate, mesoderm, and entoderm shown in Fig. 22 resembles strikingly the conditions in *Amphioxus* (Fig. 20 A).

Birds.—Due to the modified gastrulation in reptiles, birds, and mammals through the influence of yolk, a structure known as the primitive streak becomes important. An account of its formation and significance based on conditions found in the bird may be introduced conveniently at this place.

Shortly after the formation of entoderm there appears in the median line at the more caudal portion

of the blastoderm an elongated opaque band (Fig. 23). Along this *primitive streak*, which is at first merely a linear ectodermal thickening, there forms a shallow *primitive groove*, bounded laterally by *primitive folds*. At its forward end the groove enters a depression, the *primitive pit*. In front of this pit the streak ends in a knob, the *primitive knot*, or *node* (of Hensen).

The primitive streak becomes highly significant when interpreted in the light of the *theory of conrescence*, a theory of general application in vertebrate development. It will be remembered that the entoderm of birds arises by a rolling under of the outer layer along the caudal margin of the blastoderm. As the blastoderm expands, it is believed that a middle point on this margin remains fixed while the edges of the margin on each side are carried caudad and brought together. Thus, a crescentic margin is transformed into a longitudinal slit, as in Fig. 24. Since this marginal lip originally bounded the blastopore (p. 29), the longitudinal slit must also be an elongated blastopore whose direction has merely been changed.

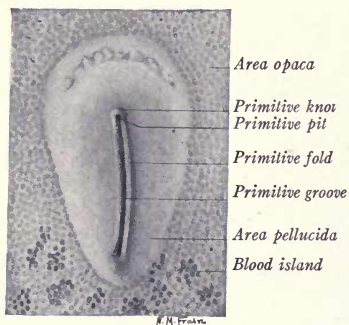


FIG. 23.—Blastoderm of a chick embryo at the stage of the primitive streak and groove (16 hours). $\times 20$.

The lips of the slit fuse, forming the primitive streak. The primitive groove may be interpreted as a further futile attempt at invagination in the region of the blastopore. The teachings of comparative embryology support these conclusions, for the neurenteric canal arises at the cranial end of the primitive streak, the anus at its caudal end, while the primary germ layers fuse in its substance. All these relations exist at the blastopore of the lower animals.

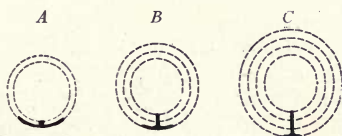


FIG. 24.—Diagram elucidating the formation of the primitive streak (Duval in Heisler). The increasing size of the blastoderm during development is indicated by dotted circular lines. The heavy line represents the crescentic groove from which the primitive streak arises by the fusion of its edges.

From the thickened ectoderm of the primitive streak a proliferation of cells takes place and there grows out laterally and caudally between the ectoderm and entoderm a solid plate of mesoderm (Fig. 31 B, C). This soon splits into somatic and splanchnic layers (Fig. 34). An axial growth, the *head process*, or *notochordal plate*, likewise extends forward from the primitive knot (Figs. 25 and 30). This fuses at once with the entoderm and from its sides grow out lateral wings of mesoderm (Fig. 31 A).

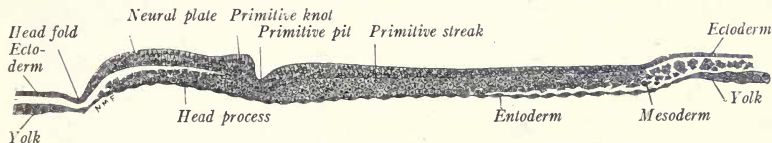


FIG. 25.—Median longitudinal section of a chick embryo at the stage of the primitive streak and head process. $\times 100$.

Since the primitive streak and groove represent a modified blastopore, it is evident that this cranial extension, the head process, corresponds to the pouchlike invagination concerned in the formation of notochord and mesoderm in reptiles. In birds the fusion of the head process with the entoderm, the relation of mesodermal sheets to it laterally, the formation of the notochord from its tissue and the occasional traces in it of a cavity continuous with the primitive pit (that is, a notochordal, or neurenteric canal), all recall the conditions described for the less modified invagination in reptiles.

Mammals.—On the blastoderm of mammals appear a primitive streak and knot essentially as in birds (Figs. 26 *A* and 28). Similarly, from the keel-like ectodermal thickening of the primitive streak mesoderm grows out laterally and caudally, and from the primitive knot there is continued forward a *head process*. All three primary germ layers fuse in the primitive knot, this condition being known in man. The head process of many mammalian embryos contains a cavity (*notochordal canal*), which in some cases is of considerable size, opening at the primitive pit. As in reptiles, the floor of this cavity fuses with the entoderm and the two rupture and disappear. A still persistent portion of the floor is shown in Fig. 27. Thus a *notochordal canal*, later enclosed by the neural folds, and then known as the *neurenteric canal*, puts the dorsal surface of the blastoderm

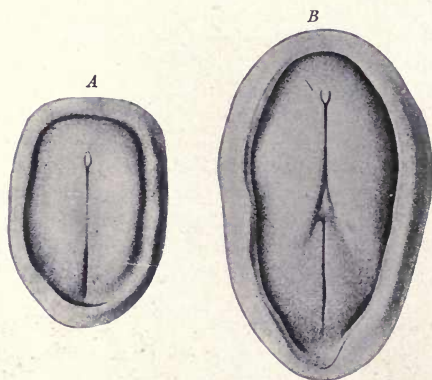


FIG. 26.—Early blastoderms of pig embryos (Keibel). $\times 20$. *A*, Embryo with primitive streak and primitive knot; *B*, a later embryo in which the neural groove is also present, cephalad in position.

into communication with the enteric cavity beneath the entoderm (Figs. 77 and 78). The roof of the head process, or notochordal canal, is for a time closely associated with the mesoderm and entoderm (compare these relations in reptiles, Fig. 22), but it eventually becomes the *notochord*.

The extent of mesoderm in rabbit embryos is shown in Fig. 28. Cranial to the primitive knot the notochord is differentiated in the mid-plane, and the mesoderm extends laterally as two wings. The mesoderm rapidly grows around the wall of the blastodermic vesicle until it finally surrounds it and the two wings fuse ventrally (Fig. 29). The single sheet of mesoderm soon splits into two layers, the cavity between being the *cælom*, or body cavity. The outer mesodermal layer (somatic), with the ectoderm, forms the *somatopleure*, or body wall; the inner splanchnic

layer, with the entoderm, forms the intestinal wall, or *splanchnopleure*. The neural tube having in the meantime arisen from the neural folds of the ectoderm, there is present the ground plan of the vertebrate body, the same in man as in *Amphioxus*.

No stages of gastrulation or mesoderm formation have yet been observed in the human embryo, but the primitive streak may be recognized

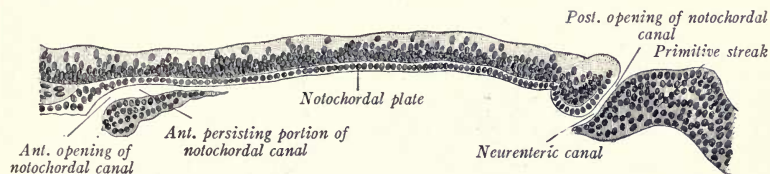


FIG. 27.—Median longitudinal section through the blastoderm of a bat (*Vesperilio murinus*) (after Van Beneden).

in later stages (Fig. 77), and there is evidence also of a transient opening, the neurenteric canal, leading from the exterior into the cavity of the primitive gut (archenteron). In *Tarsius*, an animal classed by Hubrecht with the primates, the mesoderm has two sources: (1) From the splitting of ectoderm at the caudal edge of the blastoderm; this forms the *extra-*

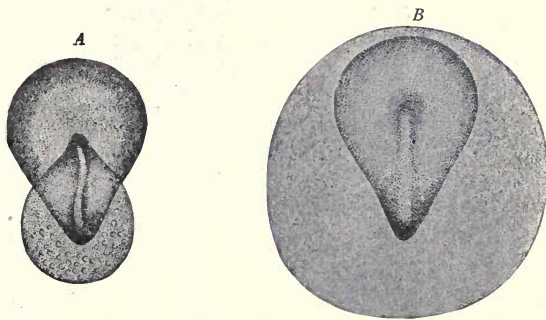


FIG. 28.—Diagrams showing the spread of mesoderm in rabbit embryos (Kölliker). In A the mesoderm is represented by the pear-shaped area about the primitive streak at the caudal end of the embryonic disc; in B, by the circular area which surrounds the embryonic disc.

embryonic mesoderm and takes no part in forming the body of the embryo. (2) The *intra-embryonic mesoderm*, which gives rise to body tissues, takes its origin from the primitive streak as in the chick and lower mammals. The origin of mesoderm in the human embryo is probably much the same as in *Tarsius*.

The Notochord or Chorda Dorsalis.—Unlike in *Amphioxus* and amphibia, the head (notochordal) process and mesoderm of higher vertebrates are not clearly of entodermal origin, but are derived from the ectoderm, any union with the entoderm being secondary. As the primitive streak recedes caudalward during development the head process is progressively lengthened at the expense of the former. Ultimately the primitive streak becomes restricted to the tail region, whereas the entire

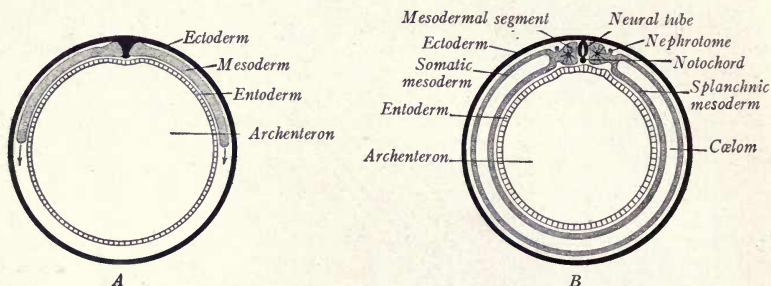


FIG. 29.—Diagrams showing the origin of the germ layers of mammals as seen in transverse section (modified from Bryce).

remainder of the body is built up around the head process as an axis. In later stages, the rod-like notochord extends in the midline beneath the neural tube from the tail to a dorsal out-pocketing of the oral entoderm, known as Seessel's pouch (p. 83). It becomes enclosed in the centra of the vertebræ and in the base of the cranium, and eventually degenerates. In *Amphioxus* it forms the only axial skeleton and it is persistent in the axial skeleton of fishes and amphibians. In man, traces of it are found as pulpy masses (*nuclei pulposi*) in the intervertebral discs.

CHAPTER III

THE STUDY OF CHICK EMBRYOS

CHICK embryos may be studied whole and most of the structures identified up to the end of the second day. The eggs should be opened in normal saline solution at 40° C. With scissors cut around the germinal disc, float the embryo off the yolk, and remove the vitelline membrane. Then float the embryo dorsal side up on a glass slide, remove enough of the saline solution to straighten wrinkles, and carefully place over the embryo a circle of tissue paper with an opening large enough to leave the germinal disc exposed. Add a few drops of fixative and float embryo into a covered dish. Following the routine technical procedure, embryos are stained and sectioned serially or mounted entire.

In the following descriptions we shall use the terms *dorsad* and *ventrad* to indicate toward the back' or 'toward the belly;' *cephalad* and *craniad* to denote 'headward;' *caudad* to denote 'tailward;' *laterad* to indicate 'toward the side;' and *mesad*, 'toward the median plane.'

EMBRYOS OF ABOUT TWENTY HOURS' INCUBATION

The events of cleavage and the formation of the three primary germ layers in birds have been described in the preceding chapter. The appearance on the disc-like blastoderm (Fig. 3) of the *primitive streak* and *groove* (Fig. 23), and its cranial extension, the *head process* (Fig. 25), has likewise received brief treatment (pp. 32-33).

In a chick embryo of twenty hours' incubation (Fig. 30), the *primitive streak* is formed as a linear opacity nearer the posterior border of the germinal disc. Over a somewhat pear-shaped clear area the yolk has been dissolved away from the overlying entoderm. This area, from its appearance, is termed the *area pellucida*. It is surrounded by the darker and more granular *area opaca*, which constitutes the remainder of the fairly sharply limited blastoderm. Whether or not the primitive streak represents the fused lips of the blastopore, it is certain that it represents the point of origin for the middle germ layer, the extent of which is indicated by the shaded area of Fig. 30. It also indicates the future longitudinal axis of the embryo. The mesoderm extends at first more rapidly caudal and lateral to the primitive streak. However, there is soon an axial growth forward from the thickened *primitive knot* (Figs. 23 and 30). This is the *head process*, or *notochordal plate*. It temporarily fuses with the entoderm (p. 33) and is continuous laterally with expanding mesodermal sheets (Figs. 25 and 31).

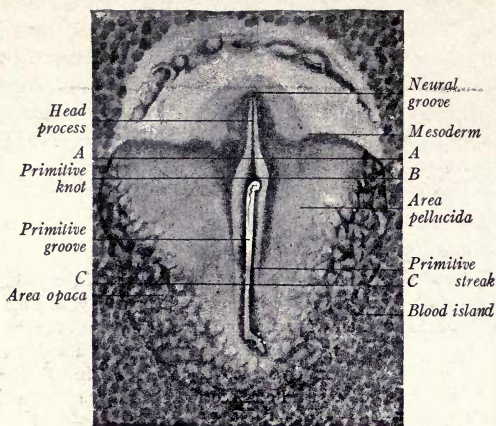


FIG. 30.—Dorsal surface view of a twenty-hour chick embryo, showing primitive streak, head process and extent of mesoderm (after Duval). $\times 17$. The lines A, B, and C indicate the levels of the corresponding sections shown in Fig. 31.

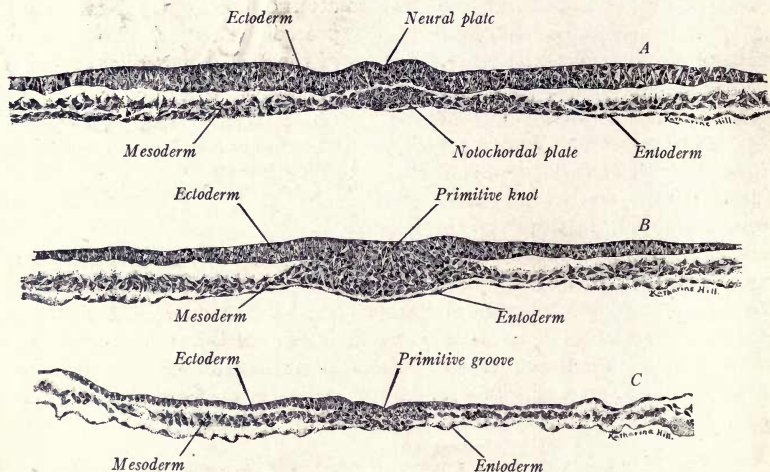


FIG. 31.—Transverse sections through the embryonic area of a twenty-hour chick. $\times 165$. A, through the head process; B, through the primitive knot; C, through the primitive streak.

A transverse section through the primitive streak at twenty hours (see guide line *C*, Fig. 30) shows the three germ layers distinct laterally (Fig. 31 *C*). In the midline, a depression in the ectoderm is the *primitive groove*. In this region there is no line of demarcation between ectoderm and mesoderm. A transverse section through the primitive knot (Fig. 31 *B*; guide line *B*, Fig. 30) shows the three germ layers intimately fused (cf. Fig. 51). There is a marked proliferation of cells, which are growing cephalad to form the *notochordal plate* (head process) (cf. Fig. 25).

A transverse section through the notochordal plate, just beginning to form at this stage (Fig. 31 *A*; guide line *A*, Fig. 30) shows the thickening in the midplane which will separate from the lateral mesoderm and form the *notochord*. It is fused with the entoderm but not with the ectoderm.

After the notochordal plate becomes prominent at twenty hours, the differentiation of the blastoderm is rapid. A curved fold, at first involving the ectoderm and entoderm alone, is formed cephalad of the notochordal process. This is the *head fold*, and is the anlage of the head of the embryo (Figs. 25 and 32). The ectoderm has thickened on each side of the mid-dorsal line, forming the *neural folds*. The groove between these is the *neural groove*. The closure of this groove will later form the *neural tube*, the anlage of the central nervous system. The notochord is now differentiated from the mesoderm and may be seen in the median plane through the ectoderm. In the mesoderm, lateral to the notochord and cephalad of the primitive knot, transverse furrows have differentiated two pairs of block-like *mesodermal segments*, one incomplete cranially. As development proceeds these increase in number, successive pairs being developed caudally. They will be described in detail later (p. 53).

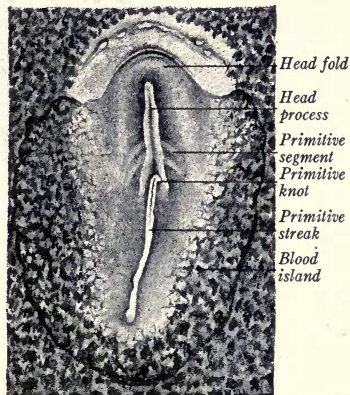


FIG. 32.—Surface view of a twenty-one hour chick embryo, in which the head fold and first two pairs of primitive mesodermal segments are present. The head process is seen through the neural groove (after Duval). $\times 13$.

EMBRYO OF SEVEN SEGMENTS (TWENTY-FIVE HOURS' INCUBATION)

In this embryo (Fig. 33) there is a prominent network of blood vessels and blood cells in the caudal portion of the *area opaca*. In its cranial portion isolated groups of blood and blood vessel-forming cells are seen

as *blood islands*. Together, they constitute the *angioblast* from which arises the extra-embryonic blood vascular system. The *area pellucida* has the form of a slipper, with broad toe directed forward. The *head fold* has become cylindrical and the head of the embryo is free for a short distance from the germinal disc. The mesoderm extends on each side beyond the head leaving a median clear space, the *proamniotic area*.

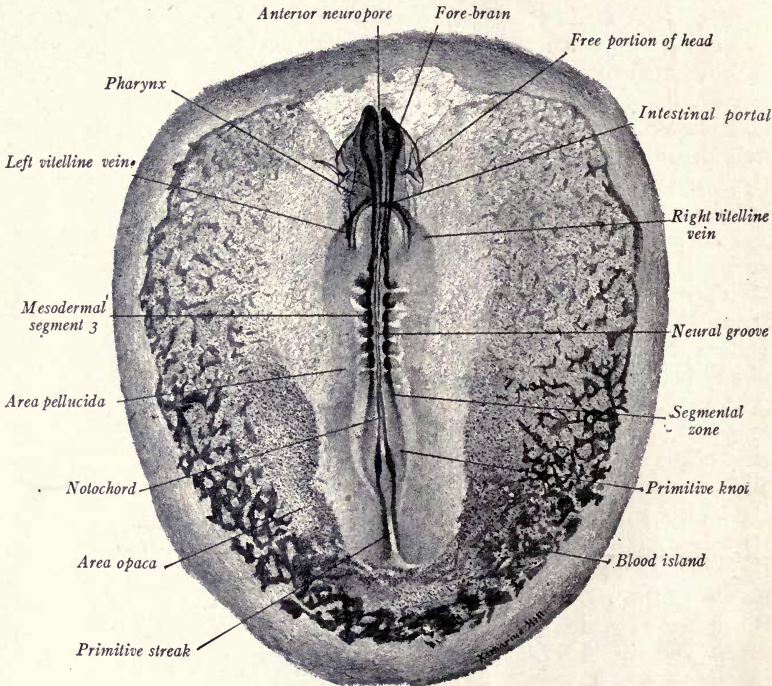


FIG. 33.—Dorsal view of a twenty-five-hour chick embryo with seven primitive segments.
 × 20.

The entoderm is carried forward in the head fold as the *fore-gut*, from which later arise the pharynx, esophagus, stomach, and a portion of the small intestine. The opening into the fore-gut faces caudad and is the *intestinal portal*. The way in which the entoderm is folded up from the blastoderm and forward into the head is shown well in a longitudinal section of an older embryo (Fig. 42). The tubular heart lies ventral to the fore-gut and cranial to the intestinal portal. In later stages it is bent to the right. Converging forward to the heart, on each side of the

portal, are the *vitelline veins*, just making their appearance at this stage. The lips of the neural folds have met throughout the cranial two-thirds of the embryo but have not fused. The *neural tube*, formed thus by the closing of the ectodermal folds, is open at either end at the *neuropores*. Cephalad, the neural tube has begun to expand to form the brain vesicles. Of these only the *fore-brain* is prominent, and from it the *optic vesicles* are budding out laterally. The paraxial mesoderm is divided by transverse furrows into seven pairs of block-like *primitive segments*. Caudally, between the segments and the primitive streak, there is the undifferentiated mesoderm of the *segmental zone*, but new pairs of segments will develop in this region. Looking through the open neural groove (*rhomboidal sinus*), one may see the *notochord* extending from the primitive knot cephalad in the midplane until it is lost beneath the neural tube in the region of the primitive segments. The *primitive streak* is still prominent at the posterior end of the area pellucida, forming about one-fourth the length of the embryo.

TRANSVERSE SECTIONS

Sections through the Primitive Streak and Knot.—Conditions are essentially the same as in the twenty-hour embryo (Fig. 31).

Section through the Fifth Primitive Segment (Fig. 34).—This general level is characterized by the differentiation of the mesoderm, the approximation of the *neural folds* and

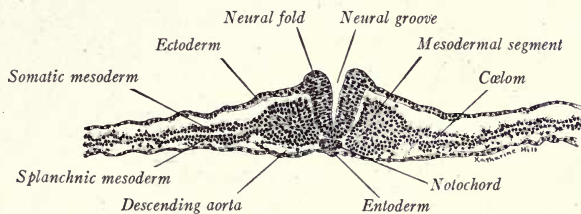


FIG. 34.—Transverse section through the fifth pair of mesodermal segments of a twenty-five-hour chick embryo. $\times 90$.

the presence of two vessels, the *descending aorta*, on each side between the mesodermal segments and the entoderm. The neural folds are thick and the ectoderm is thickened over the embryo. The *notochord* is a sharply defined oval mass of cells. The *mesodermal segments* are somewhat triangular in outline and connected by the *intermediate cell mass*, or *nephrotome*, with the lateral mesoderm. The lateral mesoderm is partially divided by irregular flattened spaces into two layers, the dorsal of which is the *somatic* layer, the ventral the *splanchnic* layer. Later, the spaces unite on either side to form the *calom*, or primitive body cavity. In the *area opaca*, more laterad than is represented in the figure, the entoderm is intimately associated with the coarsely granular *yolk*. Below the splanchnic mesoderm, *blood islands* and primitive *blood vessels* are forming; this portion of the area opaca is termed the *area vasculosa*.

Section Caudal to the Intestinal Portal (Fig. 35).—The section is characterized: (1) by the closing together of the neural folds to form the *neural tube*; (2) by the dorsal and lateral folding of the entoderm, which, a few sections nearer the head end, forms the *fore-gut*; (3) by the presence of the *vitelline veins* laterally between the entoderm and splanchnic mesothelium; (4) by the wide separation of the somatic and splanchnic mesoderm and the

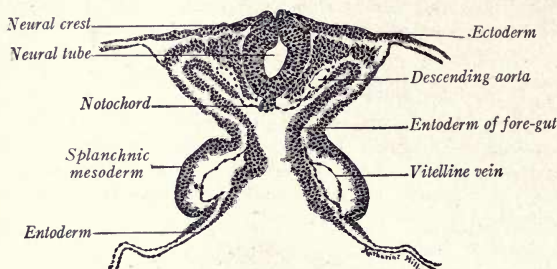


FIG. 35.—Transverse section caudal to the intestinal portal of a twenty-five-hour chick embryo. $\times 90$.

consequent increase in the size of the coelom. In this region the coelom later surrounds the heart and forms the *pleuro-pericardial cavity*.

The neural tube at this level forms the third brain vesicle, or *hind-brain*. The neural folds have not yet fused, and at their dorsal angles are the *neural crests*, the anlagen of the spinal ganglia. Mesodermal segments do not develop in this region; instead a diffuse network of mesoderm partly fills the space between ectoderm, entoderm, and mesothelium. This is termed *mesenchyme* and will be described later (p. 53).

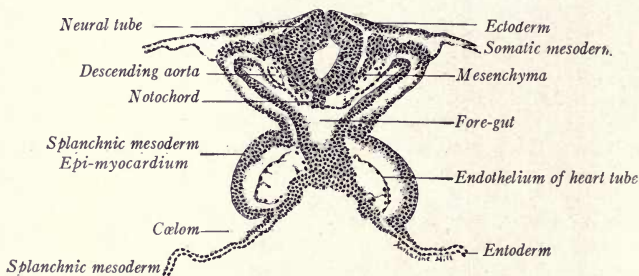


FIG. 36.—Transverse section through the intestinal portal of a twenty-five-hour chick embryo. $\times 90$.

Section through the Intestinal Portal (Fig. 36).—This section passes through a vertical fold of entoderm at the point where the latter is reflexed into the head as the *fore-gut* (cf. Fig. 42). The entoderm forms a continuous mass of tissue between the vitelline veins, thereby closing the *fore-gut* ventrally. The splanchnic mesoderm is differentiated into a thick-walled pouch on each side, lateral to the endothelial layer of the veins.

Section through the Heart (Fig. 37).—Passing cephalad in the series of sections, the vitelline veins open into the *heart* just in front of the intestinal portal. The entoderm in the head fold now forms the crescentic *pharynx* of the fore-gut, separated by the heart and splanchnic mesothelium from the entoderm of the germinal disc. The descending aortæ are larger, forming conspicuous spaces between the neural tube (*hind-brain*) and the pharynx. The heart, as will be seen, is formed by the union of *two endothelial tubes*, continuous with those constituting the vitelline veins in the preceding sections. The median walls of these tubes disappear at a slightly later stage to form a single tube, the *endocardium*. Thickened layers of splanchnic mesoderm, which, in the preceding section, invested the vitelline veins laterally, now form the mesothelial wall of the heart. In the median ventral plane, the layers of splanchnic mesoderm of each side have fused and separated from the splanchnic mesothelium of the germinal disc; thus the two pleuro-pericardial cavities are put in communication. The mesothelial wall of the heart forms the *myocardium* and *epicardium* of the adult. Dorsally, the splanchnic mesoderm, as the *dorsal mesocardium*, suspends the heart, while still more dorsally it is continuous with the somatic mesoderm.

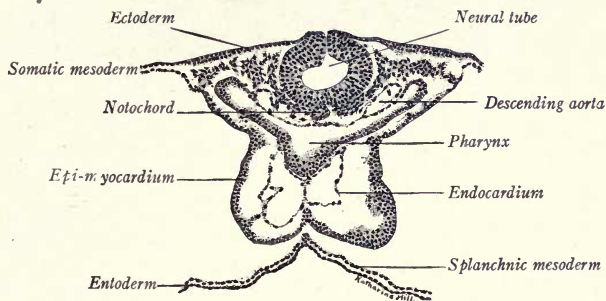


FIG. 37.—Transverse section through the heart of a twenty-five-hour chick embryo. $\times 90$.

Origin of the Primitive Heart.—From the two sections last described, it is seen that the heart arises as a pair of endothelial tubes lying in folds of the splanchnic mesoderm. Later, the endothelial tubes fuse and the mesodermal folds are also brought together. The heart then consists of a single endothelial tube within a thick-walled investment of mesoderm. The origin of the endothelial cells of the heart—whether they arise from entoderm or mesoderm—is not surely known. The vascular system is primitively a paired system, the heart arising as a double tube with two veins entering and two arteries leaving it (cf. Figs. 268 and 269).

Origin of the Blood Vessels and Blood.—We have seen that in the area opaca a network of blood vessels and blood islands is differentiated as the *angioblast*. This tissue gives rise to primitive blood vessels and blood cells and probably is derived from the splanchnic mesoderm. The vessels arise first as reticular masses of cells, the so-called *blood islands*. These cellular thickenings undergo differentiation into two cell types, the innermost becoming *blood cells*, the outermost forming a flattened *endothelial* layer which encloses the blood cells. All the primitive blood vessels of the embryo are composed of an endothelial layer only. The endothelial cells continue to divide, forming vascular sprouts and in this way new vessels are in part produced. The first vessels arising in the vascular area of a chick embryo unite into a close network, some of the branches of which enlarge to form vascular trunks. One pair of such trunks, the *vitelline veins*, is differentiated

adjacent to the posterior end of the heart and later connects with it. Another pair, the *vitelline arteries*, is developed in continuation with the aortæ of the embryo. The vessels of the vascular area thus appear before those of the embryo have developed; they probably arise from the splanchnic mesoderm, and, both arteries and veins, are composed of a simple endothelial wall. As the coelom develops in the region of the vascular area of the embryo soon after the differentiation of the angioblast, the anlagen of the blood vessels are formed only in the splanchnic layer. (For the development of the heart and blood vessels see Chapter IX.)

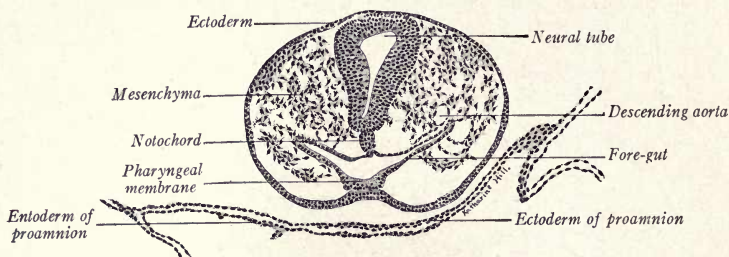


FIG. 38.—Transverse section through the pharyngeal membrane of a twenty-five-hour chick embryo. $\times 90$.

Section through the Pharyngeal Membrane (Fig. 38).—This section passes through the head fold and shows the head free from the underlying blastoderm (cf. Fig. 42). Sections a little caudad in the series prove that this is accomplished by folds of somatopleure. These bend in from the front and sides, fuse, and the head is progressively 'pinched off' from the blastoderm (see pp. 80-81). The ectoderm surrounds the head, and near the mid-ventral line it is bent dorsad, is somewhat thickened, and comes in contact with the thick entoderm of the pharynx. The area of contact between ectoderm and pharyngeal entoderm forms the *pharyngeal plate*, or *membrane*. Later, this membrane breaks through

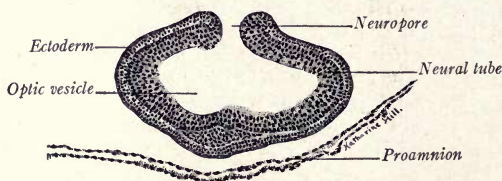


FIG. 39.—Transverse section through the fore-brain and optic vesicles of a twenty-five-hour chick embryo. $\times 90$.

and thus the oral cavity arises. The expanded neural tube is closed in this region and forms the middle brain vesicle, or *mid-brain*. The descending aortæ appear as small vessels dorsal to the lateral folds of the pharynx. The blastoderm in the region beneath the head is composed of ectoderm and entoderm only. This is the *proamniotic area*. Laterad may be seen the layers of the mesoderm.

Section through the Fore-brain and Optic Vesicle (Fig. 39).—The neural tube is open here and constitutes the first brain vesicle, or *fore-brain*. The opening is the *anterior neuropore*. The ectoderm is composed of two or three layers of nuclei and is continuous with

the much thicker wall of the fore-brain. The lateral expansions of the forebrain are the *optic vesicles*, which eventually give rise to the retina of the eye. The two ectodermal layers are in contact with each other except in the mid-ventral region, where the mesenchyma is beginning to penetrate between and separate them. The proamnion consists merely of a layer of ectoderm and of entoderm.

CHICK EMBRYO OF SEVENTEEN PRIMITIVE SEGMENTS (THIRTY-EIGHT HOURS)

The long axis of this embryo is nearly straight (Fig. 40), the area pellucida is dumb-bell shaped and the vascular network is well differenti-

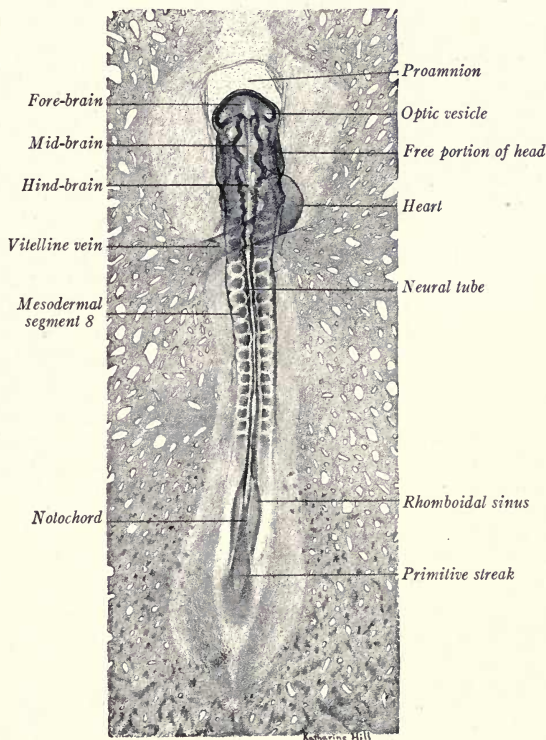


FIG. 40.—View of the dorsal surface of a thirty-eight-hour chick embryo. $\times 20$.

ated throughout the area opaca. The tubular heart is bent to the embryo's right, and opposite its posterior end the vascular network converges and becomes continuous with the trunks of the vitelline veins. Connections have also been formed between the descending aortæ and the vascular area, but as yet the vitelline arteries have not appeared as distinct trunks.

The proamniotic area is reduced to a small region in front of the head, whereas the latter is now larger and more prominent. In the posterior third of the vascular area blood islands are still prominent.

Central Nervous System and Sense Organs.—The neural tube is closed save at the caudal end where the open neural folds form the *rhomb-*

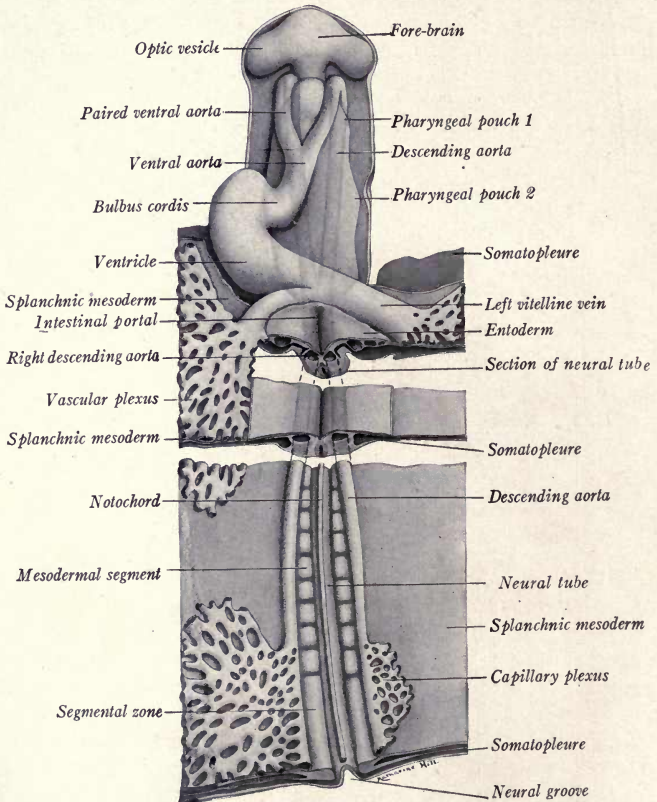


FIG. 41.—Ventral reconstruction of a thirty-eight-hour chick embryo. The entoderm has been removed except about the intestinal portal. $\times 38$.

boidal sinus. In the head the neural tube is differentiated into the three brain vesicles, marked off from each other by constrictions. The *fore-brain* (prosencephalon) is characterized by the outgrowing *optic vesicles*. The *mid-brain* (mesencephalon) is undifferentiated. The *hind-brain* (rhombencephalon) is elongated and gradually merges caudally with the

spinal cord. It shows a number of secondary constrictions, the *neuromeres*. The ectoderm is thickened laterally over the optic vesicles to form the *lens placode* of the eye (Fig. 43). The optic vesicle is flattened at this point and will soon invaginate to produce the inner, nervous layer of the retina. Dorso-laterally, in the hind-brain region, the ectoderm is thickened and invaginated as the *auditory placode* (Fig. 45). This placode later forms the *otocyst*, or *otic vesicle*, from which is differentiated the epithelium of the *internal ear* (membranous labyrinth).

Digestive Tube.—The entoderm is still flattened out over the surface of the yolk caudal to the intestinal portal. In Fig. 41 the greater part of the entoderm is cut away. The flattened fore-gut, folded inward at the portal, shows indications of three lateral diverticula, the *pharyngeal pouches*. Cephalad, the pharynx is closed ventrally by the *pharyngeal membrane*.

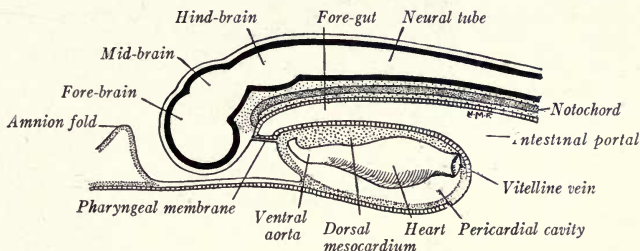


FIG. 42.—A median longitudinal section of the head of a thirty-eight-hour chick embryo.
X about 50.

Heart and Blood Vessels.—After receiving the vitelline veins cephalad of the intestinal portal, the double-walled tube of the heart dilates and bends ventrad and to the embryo's right (Fig. 41). It then is flexed dorsad and to the median plane, and narrows to form the *ventral aorta*. The aorta lies ventrad to the pharynx and divides at the boundary line between the mid- and hind-brain into two *ventral aortæ*. These diverge and course dorsad around the pharynx. Before reaching the optic vesicles they bend sharply dorsad and caudad, and, as the paired *descending aortæ*, may be traced to a point opposite the last primitive segments. In the region of the intestinal portal they lie close together and have fused to form a single vessel, the *dorsal aorta*. They soon separate, and, opposite the last primitive segments, they are connected by numerous capillaries with the vascular network. In this region, at a later stage, the trunks of the paired *vitelline arteries* will be differentiated. The heart beats at this stage; the blood flows from the vascular area by way of the vitelline veins to the heart, thence by the aortæ and vitelline arteries back again.

This constitutes the *vitelline circulation*, and through it the embryo receives nutriment from the yolk for its future development.

In studying transverse sections of the embryo it is not sufficient merely to identify the structures seen. The student should determine also the exact level of each section with respect to Figs. 40, 41 and 42, and trace the organs from section to section in the series. It is important to remember that the transverse sections figured and described in this manual (except those of the fifty-hour chick) are all drawn viewed from the cephalic surface; hence the right side of the embryo is at the reader's left.

TRANSVERSE SECTIONS

Section through the Fore-brain and Optic Vesicles (Fig. 43).—The *optic stalks* connect the *optic vesicles* laterally with the ventral portion of the *fore-brain*. Dorsally, the section passes through the *mid-brain*, due to the somewhat ventrally flexed head (cf. Fig.

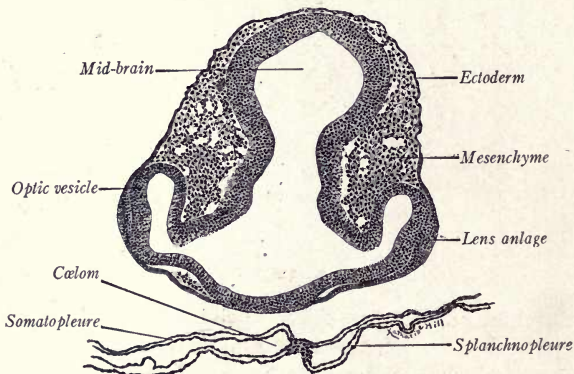


FIG. 43.—Transverse section through the fore-brain of a thirty-eight-hour chick embryo. $\times 75$.

42). We have alluded to the thickening of the *lens placode*. Note that there is now a considerable amount of mesenchyme between the ectoderm and the neural tube. Layers of mesoderm are present in the underlying blastoderm.

Section through the Pharyngeal Membrane and Mid-brain (Fig. 44).—In the mid-ventral line the thickened ectoderm bends up into contact with the entoderm of the rounded *pharynx* of the fore-gut. At this point the *oral opening* will break through. On either side of the pharynx a pair of large vessels is seen; the ventral pair are the *ventral aortæ*. Two sections cephalad their cavities open into those of the dorsal pair, the *descending aortæ*. The section is thus just caudad of the point where the ventral aortæ bend dorsad and caudad to form the descending aortæ. The section passes through the caudal end of the *mesencephalon* which is here thick walled with an oval cavity. Note the large amount of undifferentiated mesenchyme in the section. The structure of the blastoderm is complicated by the presence of collapsed blood vessels.

Section through the Hind-brain and Auditory Placodes (Fig. 45).—Besides the *auditory placodes* already described as the anlagen of the internal ear, this section is characterized by: (1) the large *hind-brain*, somewhat flattened dorsad; (2) the broad, dorso-ventrally

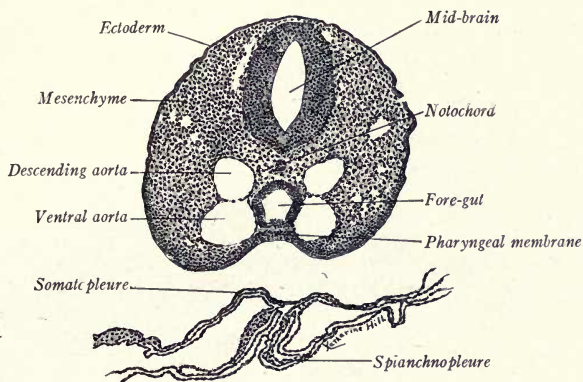


FIG. 44.—Transverse section through the pharyngeal membrane of a thirty-eight-hour chick embryo. $\times 75$.

flattened *pharynx*, above which on each side lie the *descending aortæ*; (3) the presence of the *bulbar* and *ventricular* portions of the heart. The bulbus is suspended dorsally by the mesoderm, which here forms the *dorsal mesocardium*. The ventricle lies on the right side

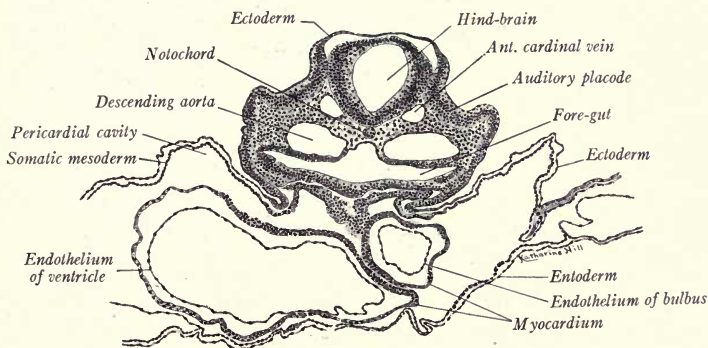


FIG. 45.—Transverse section through the hind-brain and auditory placodes of a thirty-eight-hour chick embryo. $\times 75$.

of the embryo; a few sections caudad in the series it is continuous with the ventral aorta (cf. Fig. 41). Between the *somatic* and *splanchnic mesoderm* is the large *pericardial cavity*. It surrounds the heart in this section. Dorsal to the aortæ are the *anterior cardinal veins*, which return blood from the head region.

Section through the Caudal End of the Heart (Fig. 46).—The section passes through the *hind-brain*. The descending aortæ are separated only by a thin septum which is ruptured in this section. The anterior cardinal veins are cut at the level where they bend

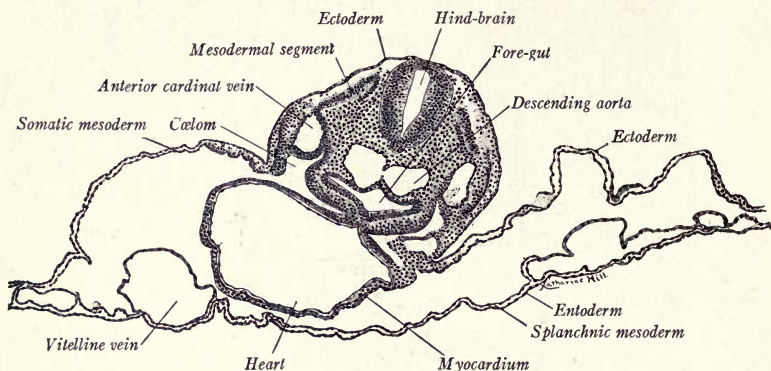


FIG. 46.—Transverse section through the caudal end of the heart of a thirty-eight-hour chick embryo. $\times 75$.

ventrad to enter the heart. The mesothelial wall of the heart is continuous with the splanchnic mesoderm. On the right side of the section there is apparent fusion between the *myocardium* of the heart and the *somatic mesoderm*. A pair of primitive *mesodermal*

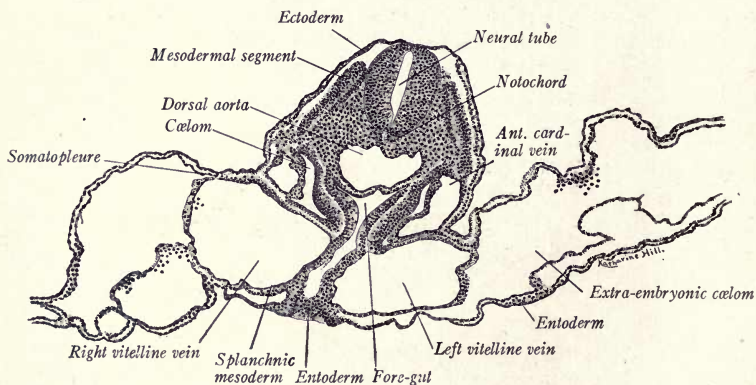


FIG. 47.—Transverse section through the intestinal portal of a thirty-eight-hour chick embryo. $\times 90$.

segments may be seen in this section lateral to the hind-brain. It may be noted here that the primitive segments were not present in the sections of the head previously studied.

Section through the Intestinal Portal (Fig. 47).—The *descending aortæ* now form a single vessel, the *dorsal aorta*, the medium septum having disappeared. The section passes through the entoderm at the point where it is folded dorsad and cephalad into the head as the *fore-*

gut (cf. Fig. 42). Two sections caudad is found the opening (*intestinal portal*) where the fore-gut communicates with the flattened open gut between the entoderm and the yolk. On each side of the fore-gut are the large *vitelline veins*, sectioned obliquely. The splanchnic mesoderm overlying these veins is pressed by them against the somatic mesoderm and the cavity of the coelom is thus interrupted on each side.

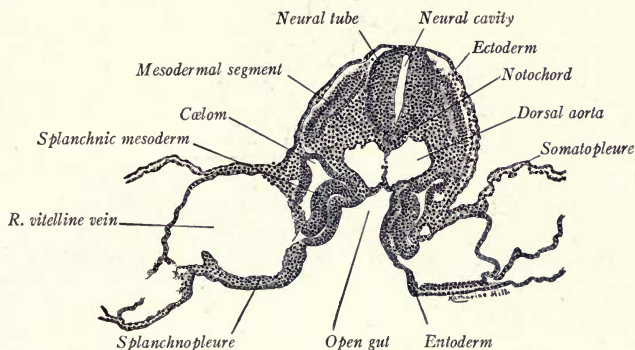


FIG. 48.—Transverse section caudal to the intestinal portal of a thirty-eight-hour chick embryo. $\times 90$.

Section Caudal to the Intestinal Portal (Fig. 48).—This section resembles the preceding save that the primitive gut is without a ventral wall. The right *vitelline vein* is still large.

Section through the Fourteenth Pair of Primitive Segments (Fig. 49).—The body of the embryo is now flattened on the surface of the yolk. Here the descending aortæ are

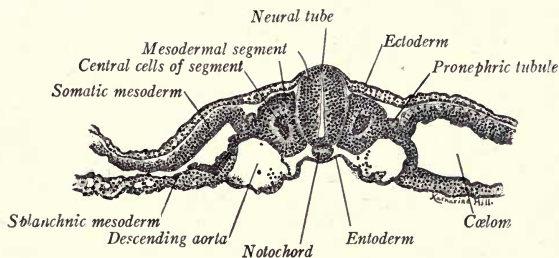


FIG. 49.—Transverse section through the fourteenth pair of mesodermal segments of a thirty-eight-hour chick embryo. $\times 90$.

still separate and occupy the depressions lateral to the primitive segments. The section is characterized by the notochord and the differentiated mesoderm which forms the primitive segments, nephrotomes, and somatic and splanchnic mesoderm. Arising from the nephrotomes are sprout-like *pronephric tubules*. The tips of these hollow out and unite to form the *primary excretory*, or *mesonephric duct*. All of these structures are described on pp. 53-54.

Section through the Rhomboidal Sinus (Fig. 50).—The *neural groove* is open, the *notochord* is oval in form. The *ectoderm* is characterized by the columnar form of its cells. At the point where the ectoderm joins the neural fold a ridge of cells projects ventrally on either side. These projecting cells form the *neural crests*, and from them the *spinal*

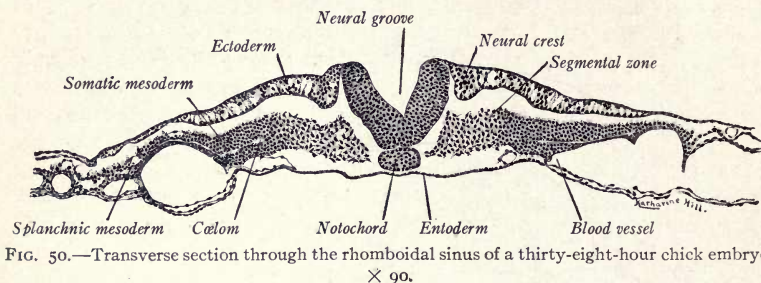


FIG. 50.—Transverse section through the rhomboidal sinus of a thirty-eight-hour chick embryo. $\times 90$.

ganglia are formed. The section is at the level of the *segmental zone*, where mesodermal segments have not formed as yet. The mesodermal plates have split laterally into layers, but the cœlomic cavities are mere slits. Between the splanchnic mesoderm and the entoderm blood vessels may be seen.

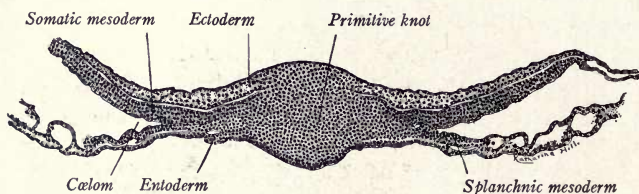


FIG. 51.—Transverse section through the primitive (Hensen's) knot of a thirty-eight-hour chick embryo. $\times 90$.

Section through the Primitive (Hensen's) Knot or Node (Fig. 51).—The section shows the three germ layers fused inseparably at the 'knot' into a mass of undifferentiated tissue. The mesoderm is split laterally into the somatic and splanchnic layers.

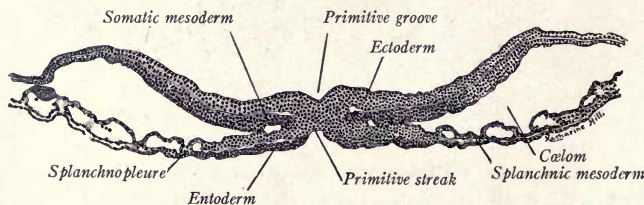


FIG. 52.—Transverse section through the primitive streak of a thirty-eight-hour chick embryo. $\times 90$.

Section through the Primitive Streak (Fig. 52).—In the mid-dorsal line is the primitive groove. The germ layers may be seen taking their origin from the undifferentiated tissue of the *primitive streak*, beneath the *primitive groove*. Laterad, between the splanchnic mesoderm and entoderm, blood vessels are present as in the preceding sections.

Mesodermal Segments.—We have seen that these are developed by the appearance of transverse furrows in the mesoderm (Fig. 53). Later, a longitudinal furrow partially separates the paired segments from the lateral unsegmented mesoderm. The segments are block-like with rounded corners when viewed dorsally, triangular in transverse sections (Figs. 49 and 53). They are formed cranio-caudally, the most cephalic being the first to appear. The first four lie in the head region. The segments contain no definite cavity, but a potential cavity representing a portion of the coelom is filled with cells, and the other cells of the segments form a thick mesothelial layer about them (Fig. 49). The ventral wall and a portion of the median wall of each primitive segment become transformed into *mesenchyma* which surrounds the neural tube and notochord (Fig. 290). The remaining portions of the segments persist as the *dermo-muscular plates*. The cells of the mesial wall of the plate, the *myotome*, elongate and give rise to the *skeletal muscle* of the body. These muscles are thus at first segmented, but later many of the segments fuse. In the trunk muscles of the adult fish the primitive segmental condition is retained.

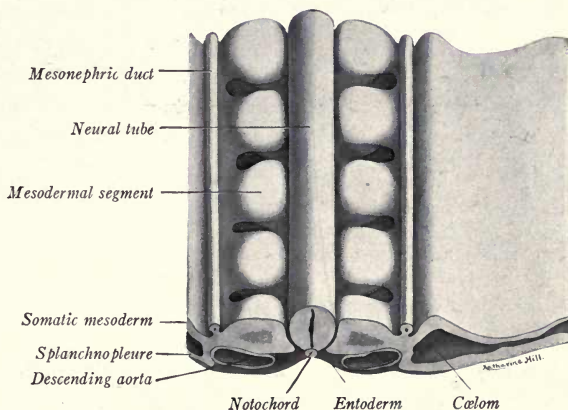


FIG. 53.—Semi-diagrammatic reconstruction of five mesodermal segments of a forty-eight-hour chick embryo. The ectoderm is removed from the dorsal surface of the embryo.

The Intermediate Cell Masses or Nephrotomes.—The bridge of cells connecting the primitive segments with the lateral mesodermal layers constitutes the *nephrotome* (Figs. 49 and 53). In the chick, the nephrotomes of the fifth to sixteenth segments give rise dorsad to pairs of small cellular sprouts, the rudimentary kidney tubules of the *pronephroi*, segmentally arranged in the furrow lateral to the primitive segments. By the union of these cell masses distally, solid cords are formed which run

lengthwise in the furrow. These cords hollow out, grow caudad, and become the *primary excretory (mesonephric) ducts* (Fig. 53). More caudally the intermediate cell masses form the embryonic kidney, or *mesonephros*, the tubules of which open into the primary excretory duct. Further details concerning these provisional kidneys are given on pages 196–200. Since the genital glands develop in connection with the mesonephros, and the kidney of the adult (metanephros) is partly developed as an outgrowth of the primary excretory duct, the intermediate cell mass may be regarded as the *anlage of the urogenital glands and their ducts*. These structures are thus of mesodermal origin.

Somatopleure and Splanchnopleure.—In the embryo of seven primitive segments the mesoderm was seen to split laterally into two layers, the *somatic* (dorsal) and the *splanchnic* (ventral) *mesoderm* (Fig. 34). These layers persist in the adult, the somatic mesoderm giving rise to the pericardium of the heart, to the parietal pleura of the thorax, and to the peritoneum of the abdomen, while the splanchnic layer forms the epicardium and myocardium of the heart, the visceral pleura of the lungs, and the mesenteries and mesodermal layer of the gut. The somatic mesoderm and the ectoderm, with the tissue developed between them, constitute the body wall, which is termed the *somatopleure*. In the same way the splanchnic mesoderm and the entoderm, with the mesenchymal tissue between them, constitute the wall of the gut, or the *splanchnopleure*.

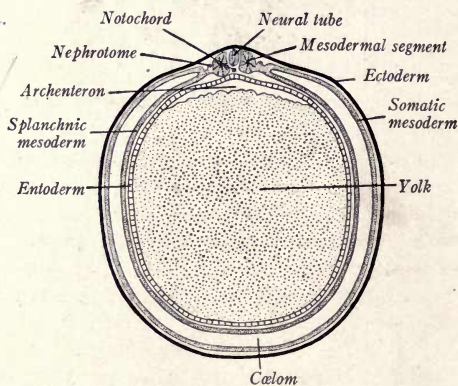


FIG. 54.—Diagrammatic transverse section of a vertebrate embryo (adapted from Minot).

Cœlom.—The cavity between the somatopleure and splanchnopleure is the *cœlom* (body cavity). With the splitting of the mesoderm, isolated cavities are produced. These unite on each side and eventually form one cavity—the cœlom. With the extension of the mesoderm, the cœlom surrounds the heart and gut ventrally (Fig. 54). Later, it is subdivided

into the *pericardial cavity* about the heart, the *pleural cavity* of the thorax, and the *peritoneal cavity* of the abdominal region. In the chick stages already studied, the embryo was flattened on the surface of the yolk and the somatopleure and splanchnopleure did not meet ventrally. If this union occurred they would conform to the structural relations shown in Fig. 54, which is essentially the ground plan of the vertebrate body.

Mesenchyme.—In the sections through the head of this embryo, and through that of the preceding stage, but four primitive segments were found. The greater part of the mesoderm in the head appears in the form of an undifferentiated network of cells which fill in the spaces between the definite layers (epithelia). This tissue is *mesenchyme* (Fig. 55). The mesoderm may be largely converted into mesenchyme, as in the head, or any of the mesodermal layers may contribute to its formation. Thus, it may be

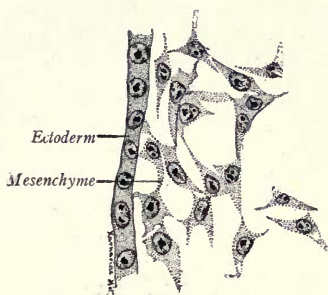


FIG. 55.—Mesenchyme from the head of a thirty-eight-hour chick embryo. $\times 495$.

derived from the primitive segments and from the somatic and splanchnic mesoderm. The cells of the mesenchyme form a syncytium, or network, and are at first packed closely together. Later, they may form a more open network with cytoplasmic processes extending from cell to cell (Fig. 55). The mesenchyme is an important tissue of the embryo; from it are differentiated the blood and lymphatic systems, together with most of the smooth muscle, connective tissue, and skeletal tissue of the body.

The body of the embryo is now composed: (1) of cells arranged in layers—*epithelia*, and (2) of diffuse *mesenchyme*. The term 'epithelium' is used in a general sense. Those epithelial layers lining the body cavities are termed *mesothelia*, while those lining the blood vessels and lymphatics are called *endothelia*.

Derivatives of the Germ Layers.—The tissues of the adult are derived from the epithelia and mesenchyme of the three germ layers as follows:

<i>Ectoderm</i>	<i>Mesoderm</i>	<i>Entoderm</i>
1. Epidermis and its derivatives (hair, nails, glands).	A. Mesothelium. 1. Pericardium.	1. Epithelium of digestive tract.
2. Conjunctiva and lens of eye.	2. Pleura. 3. Peritoneum.	2. Liver. 3. Pancreas.
3. Sensory epithelia of organs of special sense.	4. Serous layer of intestine.	4. Epithelium of pharynx.
4. Epithelium of mouth, enamel of teeth, oral glands. Hypophysis.	5. Epithelium of most of urogenital organs.	Eustachian tube. Tonsils.
5. Epithelium of anus.	6. Striated muscle. 1. Skeletal. 2. Cardiac.	Thymus. Thyroid. Parathyroids.
6. Male urethra (distad).	B. Mesenchyme.	5. Epithelium of respiratory tract.
7. Epithelium of amnion and chorion.	1. Blood cells. 2. Bone marrow.	Larynx. Trachea.
8. Nervous, neuroglia, and chromaffin cells of nervous system.	3. Endothelium of blood vessels and lymphatics.	Lungs.
9. Smooth muscle of sweat glands and of iris.	4. Lymphoid organs and suprarenal cortex.	6. Epithelium of most of bladder, of female urethra, male prostatic urethra and prostate.
10. Notochord.	5. Supporting tissues. (Connective tissue, cartilage and bone.	7. Notochord.
	6. Smooth muscle.	

CHICK EMBRYO OF TWENTY-SEVEN SEGMENTS (FIFTY HOURS)

This embryo, of nearly fifty hours' incubation, lies in the center of the vascular area and is peculiar in that the head is twisted 90° to the right. In a dorsal view, therefore, one sees the right side of the head but the dorsal side of the body. In the region of the mid-brain is a very marked bend, the *cephalic flexure*. Below the head, and ventral in position, lies the tubular heart, now bent in the form of a letter S. Dorsal to the heart, in the region of the pharynx, three transverse grooves or slits may be seen. These are the *branchial grooves*, or *gill slits*. The head of the embryo is now covered by a double fold of the somatopleure, the *head fold* of the *amnion*. It envelops the head like a veil. Caudally, a fold and opacity mark the position of the *tail bud*, from which develops the caudal end of the body. The curved fold embracing this is the *tail fold* of the amnion, which will eventually meet the head fold and completely envelop the embryo.

Central Nervous System and Sense Organs (Fig. 57).—Cephalad, the neural tube is divided by constrictions into four vesicles. The fore-brain of the previous stage is now subdivided into two regions, the *telen-cephalon* and *diencephalon*. The cephalic flexure has been established

in the region of the mesencephalon. The hind-brain, as yet undivided, equals the combined length of the other three vesicles. As the lens of the eye invaginates, the wall of the optic vesicle folds inward, thus forming a double-walled structure, the *optic cup*. The auditory placode has become a sac, the *otocyst*, which overlies the hind-brain opposite the second

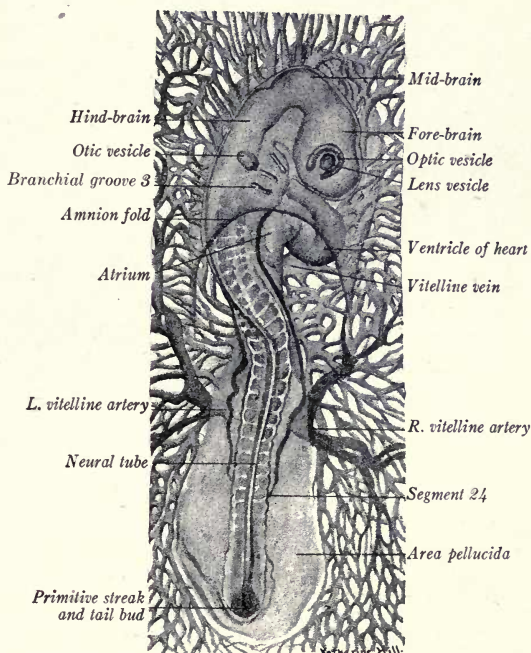


FIG. 56.—Dorsal view of a fifty-hour chick embryo, stained and mounted in balsam. $\times 14$.

branchial groove and is still connected with the outer ectoderm, cut away in Fig. 57. The rhomboidal sinus is still open at the caudal end of the neural tube.

Digestive Canal (Fig. 57).—In a reconstruction from the ventral side, the digestive canal shows differentiation into three regions. Of these, the *fore-gut* has been seen in earlier stages. A greater part of the *mid-gut* has been cut away to show the underlying structures; it is without a ventral wall and overlies the yolk. Caudad, a small portal leads into the *hind-gut* which is just beginning to evaginate into the tail fold. The pharyngeal membrane now lies in a considerable cavity, the *stomodæum*,

formed by the invaginated ectoderm. The median, ectodermal pouch next the brain wall is known as *Rathke's pouch* and is the anlage of the anterior lobe of the *hypophysis*. The pharynx shows laterally three out-pocketings, of which the first is wing-like and is the largest. These *pharyngeal pouches* occur opposite the three *branchial grooves* and here entoderm

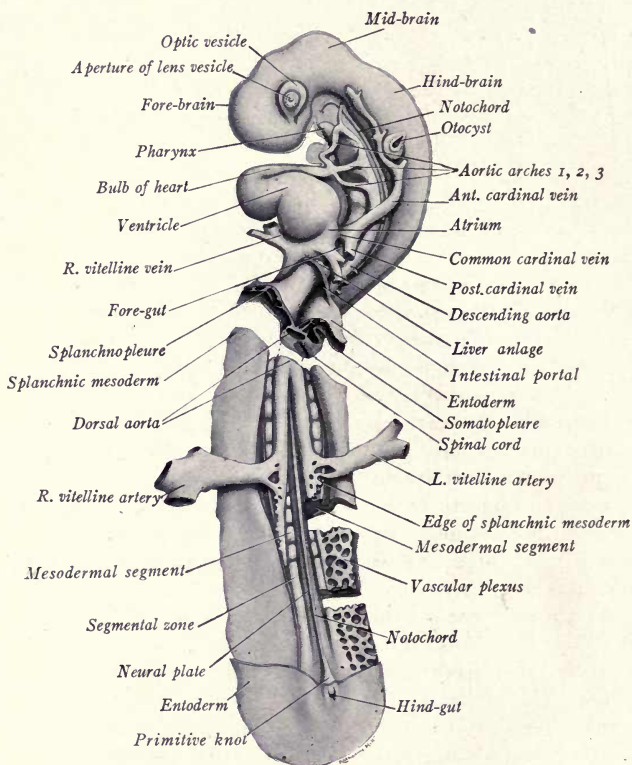


FIG. 57.—Semi-diagrammatic reconstruction of a fifty-hour chick embryo, in ventral view. $\times 18$. The entoderm has been removed save in the region of the intestinal portal and hind-gut. Owing to the torsion of the embryo, the cranial third of the embryo is seen from the left side, the caudal two-thirds in ventral view.

and ectoderm are in contact, forming the *closing plates*. At about this stage the first closing plate ruptures, thereby forming a free opening, or *branchial cleft*, into the pharynx. Between the pouches are developed the *branchial arches*, in which course the paired *aortic arches*. Toward the intestinal portal the fore-gut is flattened laterally, and before it opens out

into the mid-gut there is budded off ventrally a bilobed structure, the anlage of the *liver* (Figs. 57 and 63). It lies between the vitelline veins, and in its later development the veins are broken up into the *sinusoids*, or blood spaces of the liver.

Just as the entoderm participates in the head fold to form the fore-gut, so in the tail fold it forms the hind-gut. This at once gives rise to a tubular outgrowth which becomes the *allantois*, one of the fetal membranes to be described later (Fig. 70).

Blood Vascular System.—The tubular heart is flexed in the form of a letter S, when seen from the ventral side (Fig. 57). Four regions may be distinguished: (1) the *sinus venosus*, into which the veins open; (2) a dilated dorsal chamber, the *atrium*; (3) a tubular ventral portion flexed in the form of a U, of which the left limb is the *ventricle*, the right limb (4) the *bulbus cordis*. From the bulbus is given off the *ventral aorta*. There are now developed three pairs of *aortic arches* which open into the paired descending aortæ. The first aortic arch passes cranial to the first pharyngeal pouch and is the primitive arch seen in the thirty-eight-hour embryo. The second and third arches course on either side of the second pharyngeal pouch. They are developed by the enlargement of channels in primitive capillary networks between ventral and descending aortæ. Opposite the sinus venosus, the paired aortic trunks fuse to form the single *dorsal aorta* which extends as far back as the fifteenth pair of primitive segments. At this point the aortæ again separate, and, opposite the twentieth segments, each connects with the trunk of a *vitelline artery* which was developed in the vascular area and conveys the blood to it (Fig. 57). Caudal to the vitelline arteries the dorsal aortæ rapidly decrease in size and soon end.

As in the previous stage, the blood is conveyed from the vascular area to the heart by the *vitelline veins*, now two large trunks. In the body of the embryo there have developed two pairs of veins. In the head have appeared the *anterior cardinal veins*, already of large size and lying lateral to the ventral region of the brain vesicles (Fig. 60). Caudal to the atrium of the heart, two small *posterior cardinal veins* are developed. They lie in the mesenchyma of the somatopleure, laterad in position (Fig. 63). Opposite the sinus venosus the anterior and posterior cardinal veins of each side unite and form the *common cardinal veins* (ducts of Cuvier) which open into the dorsal wall of the sinus venosus (Fig. 57). The primitive veins are thus paired like the arteries, and like them develop by the enlargement of channels in a network of capillaries.

The following series of transverse sections from an embryo of this stage shows the more important structures. The approximate plane and level of each section may be ascertained by referring to Figs. 56 and 57.

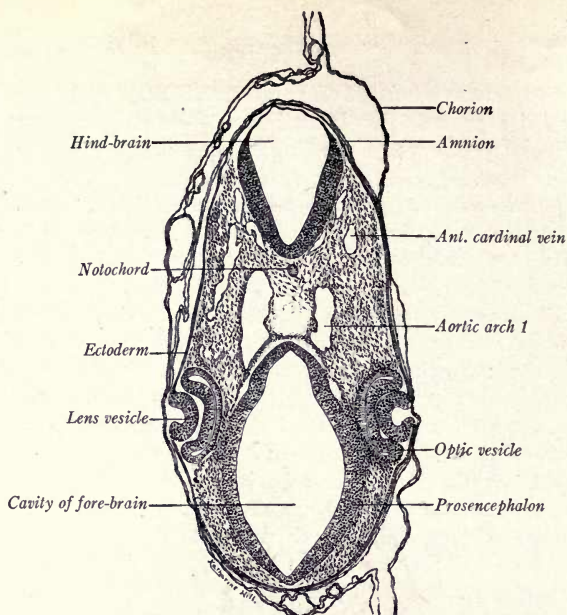


FIG. 58.—Transverse section through the fore-brain and eyes of a fifty-hour chick embryo. $\times 50$.

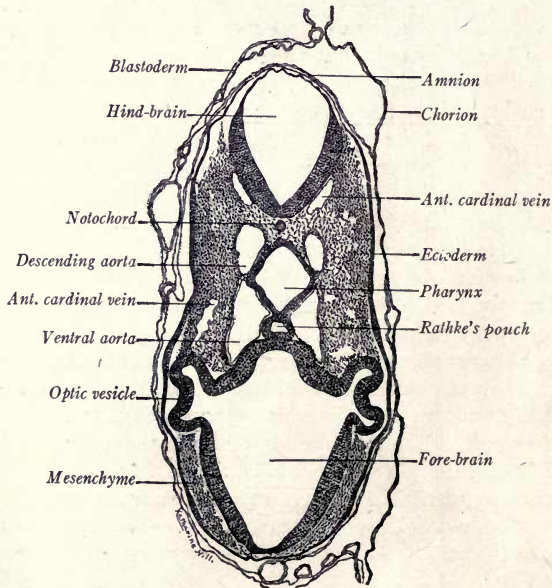


FIG. 59.—Transverse section through the optic stalks and hypophysis of a fifty-hour chick embryo. $\times 50$.

TRANSVERSE SECTIONS

Section through the Fore-brain and Eyes (Fig. 58).—The section passes in front of the optic stalks, consequently the optic vesicles appear unconnected with the fore-brain. The thickened ectoderm is invaginated to form the anlagen of the *lens vesicles*. The thicker wall of the *optic vesicles* next the lens anlage will give rise to the nervous layer of the retina; the thinner outer wall becomes the pigment layer of the retina. Ventrad in the section are the wall and cavity of the *fore-brain*, dorsad the *hind-brain* with its thin, dorsal *ependymal layer*. Between the brain vesicles on either side are sections of the *first aortic arches*, and lateral to the hind-brain are the smaller, paired *anterior cardinal veins*, which convey the blood from the head to the heart. The splanchnopleure of the blastoderm is characterized in this and subsequent sections by the presence of blood vessels in its mesodermal layer.

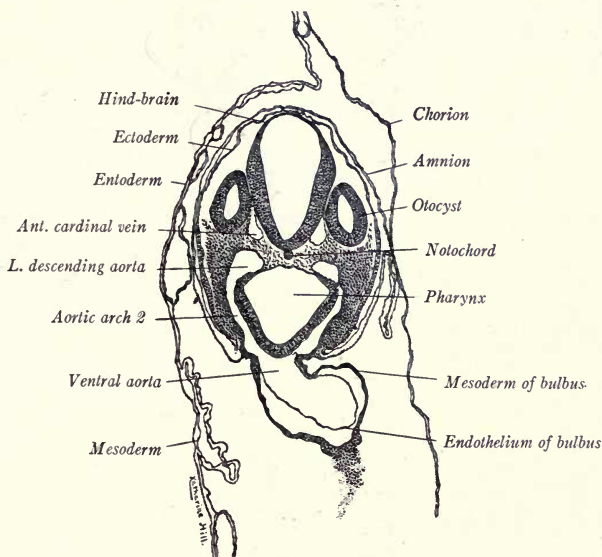


FIG. 60.—Transverse section through the otic vesicles and second aortic arches of a fifty-hour chick embryo. $\times 50$.

Section through the Optic Stalks and Hypophysis (Fig. 59).—The section passes just caudal to the lens. The *optic vesicles* are connected with the wall of the *fore-brain* by the *optic stalks*, which later form the path by which the fibers of the optic nerve pass from the retina to the brain. Both the *ventral* and the *descending aortæ* are seen in section about the cephalic end of the pharynx. Between the ventral wall of the fore-brain and the pharynx is an invagination of the ectoderm, *Rathke's pouch* (anterior lobe of the hypophysis).

Section through the Otocysts and Second Aortic Arch (Fig. 60).—The *otic vesicles* are sectioned caudal to their apertures and appear as closed sacs, lateral to the wall of the hind-brain. The cavity of the *pharynx* is somewhat triangular and its dorsal wall is thin.

The *anterior cardinal veins* pass between the otocysts and the wall of the hind-brain. Ventral to the pharynx, the *bulbus cordis* is sectioned obliquely where it leaves the heart, and at this level gives off laterad the second pair of *aortic arches* which connect dorsad with the descending aortæ. Surrounding the bulbus cordis is the large *pericardial cavity*. The student should note that in the sections of this stage so far studied, the *mesenchyme* of the head is undifferentiated, the tissues peculiar to the adult not yet having been formed.

Section through the Second Pharyngeal Pouches and Thyroid Anlage (Fig. 61). As this section is taken at a level between the second and third aortic arches, the descending aortæ and heart are unconnected. Tangential shavings have been cut from the walls of the *otocysts*. Extending laterally from the pharynx are the second pair of *pharyngeal pouches* which have already come in contact with the ectoderm to form *closing plates*.

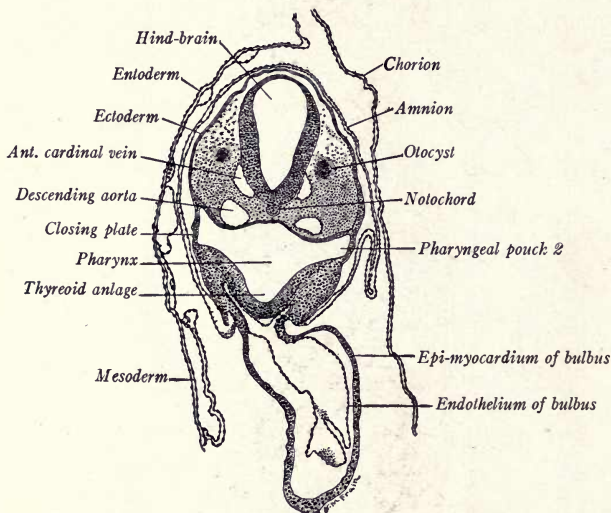


FIG. 61.—Transverse section through the second pharyngeal pouches and thyroid anlage of a fifty-hour chick embryo. $\times 50$.

A pocket-like depression in the mid-ventral floor of the pharynx represents the *thyroid anlage*; later it becomes saccular and loses its connection with the pharyngeal entoderm. The splanchnic mesodermal wall of the heart is destined to give rise later to the epi- and myocardium.

Section through the Sinus Venosus and Common Cardinal Veins (Fig. 62).—At this level, the common trunk formed by the anterior and posterior cardinal veins opens into the thin-walled *sinus venosus*. The sinus receives all of the blood passing to the heart and is separated only by a slight constriction from the larger *atrium*. The *muscle plates* of the first mesodermal segments are seen, and the *descending aortæ* have united to form a single dorsal vessel. On either side of the pharynx are subdivisions of the coelom which will form the *pleural cavities*. These cavities are separated from the pericardial cavity by the

septum transversum (anlage of diaphragm) in which the common cardinal veins cross to the sinus venosus.

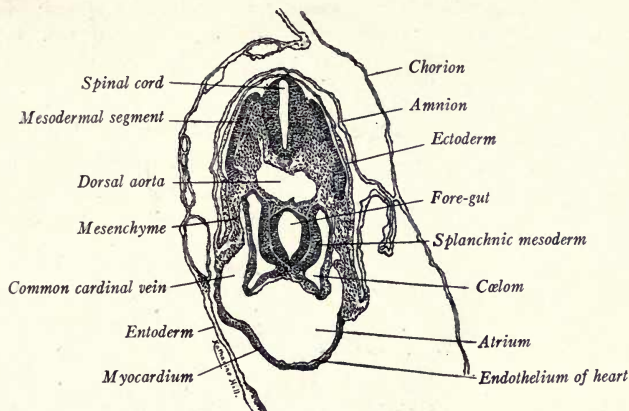


FIG. 62.—Transverse section through the sinus venosus and common cardinal veins of a fifty-hour chick embryo. $\times 50$.

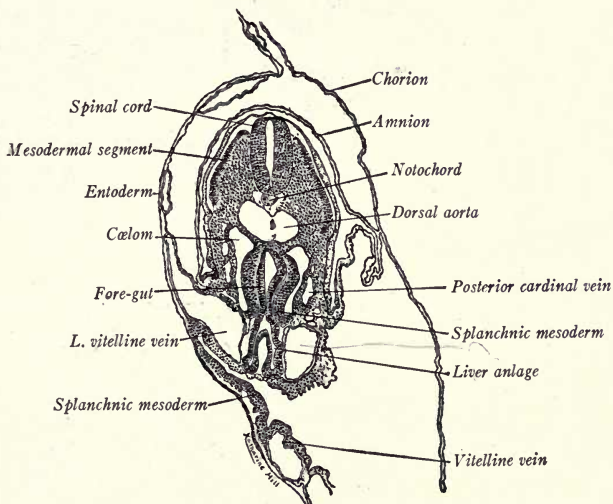


FIG. 63.—Transverse section through the anlage of the liver of a fifty-hour chick embryo. $\times 50$.

The somatopleuric folds of the amnion envelop the right side of the embryo, and the ectoderm of these folds now forms the outer layer of the *chorion* and the inner layer of the *amnion*. The mesodermal components of the folds have not yet united.

Section through the Anlage of the Liver (Fig. 63).—In this section the cavity of the fore-gut is narrow, the gut being flattened from side to side. Ventrad there are evaginated from the entoderm two elongate diverticula which form the anlagen of the *liver*. On either side of the anlagen of the liver are sections of the *vitelline veins* on their way to the sinus

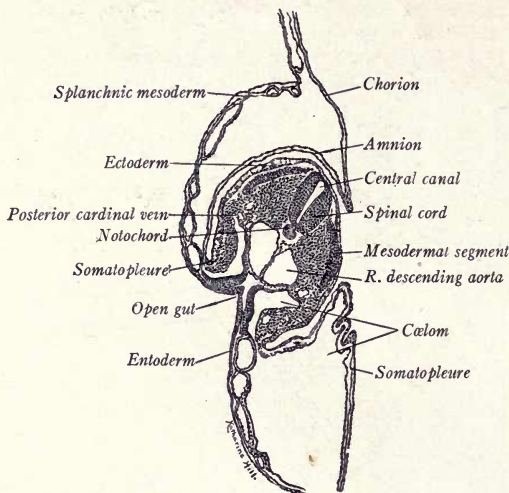


FIG. 64.—Transverse section through the cranial portion of the open intestine of a fifty-hour chick embryo. $\times 50$.

venosus at a higher level in the series. Note the intimate relation between the entodermal epithelium of the liver and the endothelium of the vitelline veins. In later stages, as the liver anlagen branch, there is, as Minot aptly expresses it, “an interescence of the entodermal cells constituting the liver and of the vascular endothelium” of the vitelline veins.

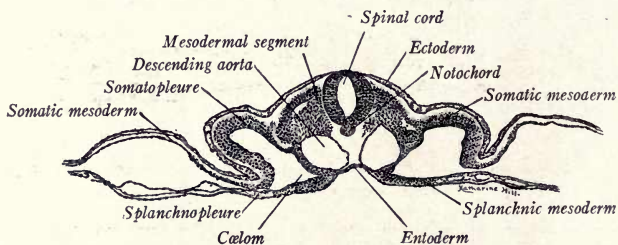


FIG. 65.—Transverse section through the seventeenth pair of mesodermal segments of a fifty-hour chick embryo. $\times 50$.

Thus are formed the hepatic *sinusoids* of the portal system, which surround the cords of hepatic cells.

The *septum transversum* is still present at this level and lateral to the fore-gut are small body cavities. Lateral to the body cavities appear branches of the *posterior cardinal veins*.

Section through the Cranial Portion of the Open Intestine (Fig. 64).—The intestine is now open ventrad, its splanchnopleure passing directly over to that of the vascular area. The folds of the *amnion* do not join, leaving the amniotic cavity open. The dorsal aorta is divided by a septum into its primitive components, the *right* and *left descending aortæ*. Lateral to the aortæ are the small *posterior cardinal veins*. The coelom is in communication with the extra-embryonic body cavity.

Section through the Seventeenth Pair of Mesodermal Segments (Fig. 65).—The body of the embryo is now no longer flexed to the right. On the left side of the figure, the

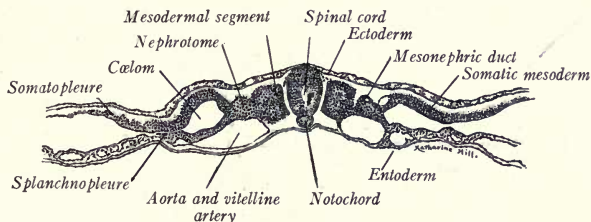


FIG. 66.—Transverse section of a fifty-hour chick embryo, at the level of the origin of the vitelline arteries. $\times 50$.

mesodermal segment shows a dorso-lateral *myotome plate*. The median and ventral portion of the segment is being converted into mesenchyme. On the right side appears a section of the *primary excretory*, or *mesonephric duct*. The embryonic *somatopleure* is arched and will form the future ventro-lateral body wall of the embryo. The lateral infoldings of the somatopleure give indication of the later approximation of the ventral body walls, by which the embryo is separated from the underlying layers of the blastoderm.

Section through the Origin of the Vitelline Arteries (Fig. 66).—At this level the embryo is more flattened and simpler in structure, the section resembling one through the

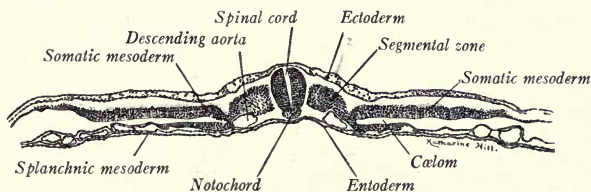


FIG. 67.—Transverse section of a fifty-hour chick embryo through the segmental zone, caudal to the mesodermal segments. $\times 50$.

mid-gut region of a thirty-eight-hour chick (Fig. 49). The amniotic folds have not appeared. On the left side of the figure the *vitelline artery* leaves the aorta. On the right side the connection of the vitelline artery with the aorta does not show, as the section is cut somewhat obliquely. The *posterior cardinal vein* is present just laterad of the right mesonephric duct. The other structures were described in connection with Fig. 49.

Section Caudal to the Mesodermal Segments (Fig. 67).—The mesodermal segments are replaced by the *segmental zone*, a somewhat triangular mass of undifferentiated mesoderm from which later are formed the *segments* and *nephrotomes*. The *notochord* is larger,

the *aorta* smaller, and a few sections caudad they disappear. Laterally the *somatopleure* and *splanchnopleure* are straight and separated by the slit-like coelom.

Section through the Notochordal Plate, Cranial to the Hind-gut (Fig. 68).—With the exception of the ectoderm, the structures near the median plane are merged into an undifferentiated mass of dense tissue, the notochordal plate. The cavity of the *neural tube* and its dorsal outline may, however, still be seen. Laterally the segmental zone and the various layers are differentiated.

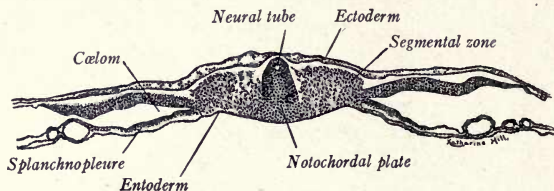


FIG. 68.—Transverse section of a fifty-hour chick embryo through the notochordal plate, cranial to the hind-gut. $\times 50$.

Section through the Hind-gut and Primitive Streak (Fig. 69).—In this embryo the caudal evagination to form the *hind-gut* has just begun. The section shows the small cavity of the hind-gut in the midplane. Its wall is composed of columnar entodermal cells and it is an outgrowth of the entodermal layer. A few sections cephalad in the series, the hind-gut opens by its own intestinal portal. Dorsal to the hind-gut may be seen undifferentiated cells of the *primitive streak*, continuous dorsad with the *ectoderm*, ventrad with the *entoderm* of the hind-gut, and laterally with the *mesoderm*.

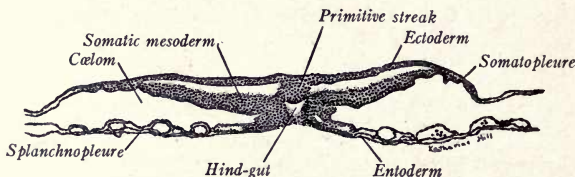


FIG. 69.—Transverse section through the hind-gut of a fifty-hour chick embryo. $\times 50$.

Extra-embryonic Structures.—In the chick embryos which we have studied, there are large areas developed which are extra-embryonic, that is, lie outside the embryo. The splanchnopleure of the area vasculosa, for instance, forms the wall of the *yolk sac*, incomplete in the early stages. The *amnion*, *chorion*, and *allantois* are extra-embryonic membranes which make their appearance at the fifty-hour stage. These structures are important in mammalian and human embryos and a description of their further development in the chick, where their structure and mode of development is primitive, will lead up to the study of mammalian embryos in which the amnion and chorion are precociously developed.

Amnion and Chorion.—These two membranes are developed in all amniote vertebrates (Reptiles, Birds, and Mammals). They are derived from the extra-embryonic somatopleure. The amnion is purely a protective structure, but the chorion of mammals has a trophic function, as through it the embryo derives its nourishment from the uterine wall. Fig. 70 A shows the amnion and chorion developing. The head fold of the somatopleure forms first and envelops the head, the tail fold makes its appearance later. The two folds extend lateral, meet and fuse (Fig. 70 B, C). The inner leaf of the folds forms the *amnion*, the remainder of the extra-embryonic somatopleure becomes the *chorion*. The actual

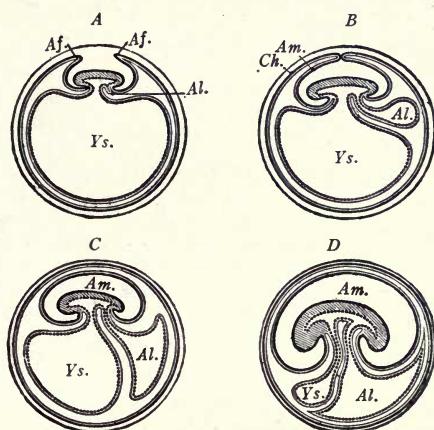


FIG. 70.—Diagrams showing the development of the amnion, chorion and allantois in longitudinal section (Gegenbaur in McMurrich). Ectoderm, mesoderm, and entoderm represented by heavy, light, and dotted lines respectively. *Af.*, Amnion folds; *Al.*, allantois; *Am.*, amniotic cavity; *Ch.*, chorion; *Ys.*, yolk sac.

appearance of these structures and their relation to the embryo have been seen in Figs. 63 and 64. The amnion, with its ectodermal layer inside, completely surrounds the embryo at the end of the third day, enclosing a cavity filled with amniotic fluid (Fig. 71). In this the embryo floats and is thus protected from injury. The chorion is of little importance to the chick. It is at first incomplete, but eventually entirely surrounds the embryo and its other appendages.

Yolk Sac and Yolk Stalk.—While the amnion and chorion are developing during the second and third day, the embryo grows rapidly. The head and tail folds elongate and the trunk expands laterally until only a relatively narrow stalk of the splanchnopleure connects the embryo with the

yolk. This portion of the splanchnopleure has grown more slowly than the body of the embryo and is termed the *yolk stalk*. It is continuous with the splanchnopleure that envelops the yolk and forms the *yolk sac*. The process of unequal growth, by which the embryo becomes separated from the blastoderm, has been falsely described as a process of constriction (see p. 80). The splanchnopleure at first forms only an oval plate on the surface of the yolk, but eventually encloses it. In Fig. 70, *C* and *D*, the relation of the embryo to the yolk sac is seen at the end of the first week of incubation. The vitelline vessels ramify on the surface of the yolk sac, and through them all the food material of the yolk is conveyed to the chick during the incubation period (about twenty-one days).

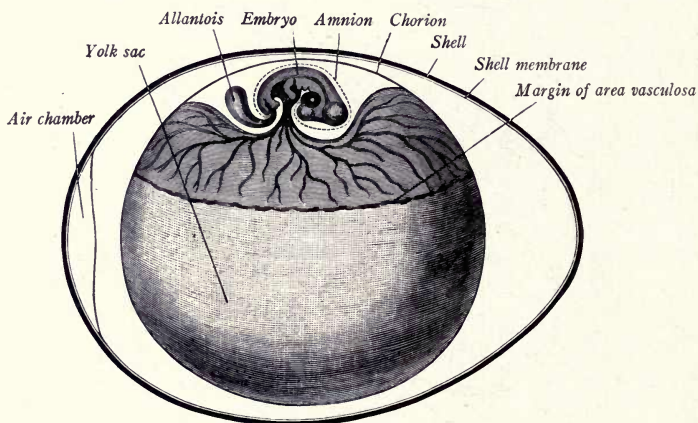


FIG. 71.—Diagram of a chick embryo at the end of the fifth day, showing amnion, chorion and allantois (Marshall). $\times 1.5$.

Allantois.—We have seen that in the fifty-hour chick a ventral evagination, the hind-gut, develops near its caudal end (Fig. 69). From it develops the anlage of the *allantois*, which, as an outgrowth of the splanchnopleure, is lined with entoderm and covered with splanchnic mesoderm (Fig. 70). It develops rapidly into a vesicle connected to the hind-gut by a narrow stalk, the *allantoic stalk*. At the fifth day the allantois is nearly as large as the embryo (Fig. 71). Its wall flattens out beneath the chorion and finally it lies close to the shell but is attached only to the embryo. The functions of respiration and excretion are ascribed to it. In its wall ramify the *allantoic vessels*, which have been compared to the *umbilical arteries* and *veins* of mammalian embryos.

The chick embryo is thus protected by the *amnion* which develops from the inner leaf of the folded somatopleure and is composed of an inner ectodermal and an outer mesodermal layer. Nutriment for the growth of the embryo is supplied by the *yolk sac* and carried to the embryo by the vitelline veins. The *allantois*, which takes its origin from the splanchnopleure of the hind-gut and is composed of an inner layer of entoderm and an outer layer of splanchnic mesoderm, functions as an organ of respiration and serves as a reservoir for the excreta of the embryonic kidneys. As we shall see, the allantois becomes more important, the yolk sac less important, in some mammals, while in human embryos both yolk sac and allantois are unimportant when compared to the *chorion*.

CHAPTER IV

HUMAN EMBRYOS AND FETAL MEMBRANES

THE fetal membranes of mammals include the *amnion*, *chorion*, *yolk sac*, and *allantois*, structures which we have seen are present in chick embryos. Most important in mammals is the manner in which the embryo becomes attached to the uterine wall of the mother, and in this regard mammalian embryos fall into two groups. Among the *Ungulates*, or hoofed mammals (e. g., the pig), the fetal membranes are of a primitive type, resembling those of the chick. Among *Unguiculates* (clawed animals like the bat and rabbit), including *Primates* (e. g., Man), the fetal membranes of the embryo show marked changes in development and structure.

FETAL MEMBRANES OF THE PIG EMBRYO

The *amnion* and *chorion* develop very much as in the chick embryo (Fig. 70 A, B). Folds of the somatopleure form very early and envelop the whole embryo. The amnion (Fig. 72) is a closed sac in embryos

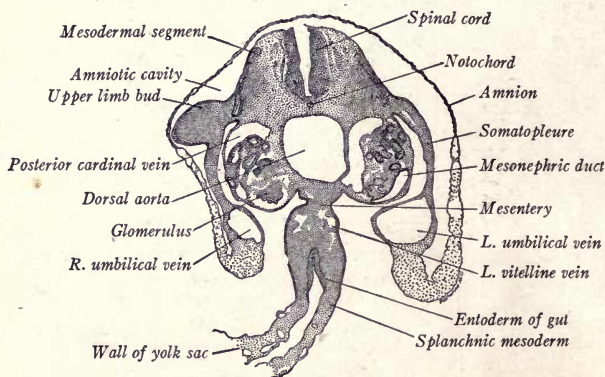


FIG. 72.—Transverse section through the yolk sac and stalk of a 5 mm. pig embryo, showing attachment of amnion.

with only a few pairs of segments, but for some time it remains attached to the chorion by a strand of tissue (Keibel). The *yolk sac* develops early, as in all mammals. In the pig it is small and the greater part of it soon degenerates. It is important only in the early growth of the embryo, its functions then being transferred to the allantois. Branches of the vitelline vessels ramify in its wall, as in that of chick embryos, but soon degenerate. The trunks of the vitelline vessels, however, persist within

the body of the embryo. The *allantois*, developing as in the chick from the ventral wall of the hind-gut (Fig. 70 A-D), appears when the embryo is still flattened out on the germinal disc. In an embryo 3.5 mm. long it is crescent-shaped and as large as the embryo. It soon becomes larger and its convex outer surface (splanchnic mesoderm) is applied to the inner surface (somatic mesoderm) of the chorion.

These surface layers fuse more or less completely. A pair of allantoic veins and arteries branch in the splanchnic layer of the allantois. These branches are brought into contact with the mesodermal layer of the cho-

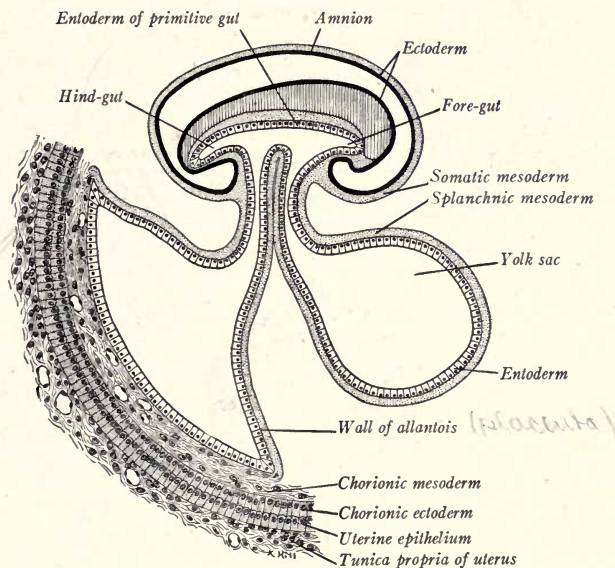


FIG. 73.—Diagram of the fetal membranes and allantoic placenta of a pig embryo, in median sagittal section (based on figures of Heisler and Minot).

rior and invade it. The outer ectodermal layer of the chorion in the meantime has closely applied itself to the uterine epithelium, the ends of the uterine cells fitting into depressions in the chorionic cells (Fig. 73). When the allantoic circulation is established, waste products given off from the blood of the embryo must pass through the epithelia of both chorion and uterus to be taken up by the blood of the mother. In the same way, nutritive substances and oxygen must pass from the maternal blood through these layers to enter the allantoic vessels. This exchange does take place, however, and thus in Ungulates the allantois has become im-

portant, not only as an organ of *respiration* and *excretion*, but as an organ of *nutrition*. Through its vessels it has taken on a function belonging to the yolk sac in birds, and we now see why the yolk sac becomes a rudimentary structure in the higher mammals. Excreta from the embryonic kidneys are passed into the cavity of the allantois which is relatively large. The name is derived from a Greek word meaning sausage-like, from its form in some animals. The *chorion* is important only as it brings the allantois into close relation to the uterine wall, but in man we shall see that it plays a more important rôle.

THE UMBILICAL CORD

Pig Embryos.—In their early development, the relation of the amnion, allantois, and yolk sac to each other and to the embryo is much the same as in the chick of five days (Fig. 71). With the increase in size of the embryo, however, the somatopleure in the region of the attachment of the amnion grows ventrad (Fig. 70 D). As a result, it is carried downward about the yolk sac and allantois, forming the umbilical cord (cf. Fig. 241). Thus, in a pig embryo 10 to 12 mm. long, the amnion is attached at a circular line about these structures some distance from the body of the embryo (cf. Fig. 119). The coelom at first extends ventrad into the cord, but later the mesodermal layers of amnion, yolk stalk, and allantois fuse and form a solid cord of tissue. This is the *umbilical cord* of fetal life and its point of attachment to the body is the *umbilicus*, or navel. The cord is covered by a layer of ectoderm continuous with that of the amnion and of the embryo, and contains, embedded in a mesenchymal (mucous) tissue: (1) the yolk stalk and (in early stages) its vitelline vessels; (2) the allantoic stalk; (3) the allantoic vessels. These latter, two arteries and a single large vein, are termed, from their position, the umbilical vessels. At certain stages (Figs. 122 and 123) the gut normally extends into the coelom of the cord, forming an umbilical hernia. Later, it returns to the coelom of the embryo and the cavity of the cord disappears. The umbilical cord of the pig is very short.

The Human Umbilical Cord.—This develops like that of the pig and may attain a length of more than 50 cm. It becomes spirally twisted, just how is not known. In embryos from 10 to 40 mm. long the gut extends into the coelom of the cord (Figs. 179 and 180). At the 42 mm. stage, the gut returns to the coelom of the body. The mucous tissue peculiar to the cord arises from mesenchyme. It contains no capillaries and no nerves, but embedded in it are the large umbilical vein, the two arteries, the allantois, and the yolk stalk. The umbilical cord may become wound about the neck of the fetus, causing its death and abortion, or by coiling about the extremities it may lead to their atrophy or amputation.

EARLY HUMAN EMBRYOS AND THEIR MEMBRANES

Descriptions of graded human embryos will introduce the reader to early mammalian development and indicate the divergencies from the chick stages already studied. A somewhat detailed account of a 4.2 mm. human embryo will then link the fifty-hour chick with the pig studies which follow.

Referring to the blastodermic vesicle of the mammal (Figs. 17 and 18), it is found to consist of an outer layer, which we have called the *trophectoderm*, and the *inner cell mass* (p. 27). The trophectoderm forms the primitive ectodermal layer of the chorion in the higher mammals and probably in man. From the inner cell mass are derived the primary ectoderm, entoderm, and mesoderm. In the earliest known human embryos, described by Teacher, Bryce, and Peters, the germ layers and amnion are present, indicating that they are formed very early. We can only infer their early origin from what is known of other mammals. The diagrams (Fig. 74 A and B) show two stages, the first hypothetical, seen in median longitudinal section. In the first stage (A) the blastodermic vesicle is surrounded by the trophectoderm layer. The inner cell mass is differentiated into a dorsal mass of ectoderm and a ventral mass of entoderm. Mesoderm more or less completely fills the space between entoderm and trophectoderm. It is assumed that as the embryo grows (B) a split occurs in the mass of ectoderm cells, giving rise to the amniotic cavity and dividing these cells into the ectodermal layer of the embryo and into the extra-embryonic ectoderm of the amnion. At the same time a cavity may be assumed to form in the entoderm, giving rise to the primitive gut. At about this stage the embryo embeds itself in the uterine mucosa. In the third stage (C), based on Peters' embryo, the extra-embryonic mesoderm has extended between the trophectoderm and the ectoderm of the amnion, and the extra-embryonic coelom appears. At first, strands of mesoderm, known as the *magma reticulare*, bridge across the coelom between the somatic and splanchnic layers of mesoderm (Fig. 76). The amniotic cavity has increased in size, and the embryo is attached to the trophectoderm by the unsplit layer of mesoderm between the ectoderm of the amnion and the trophectoderm of the chorion. The latter shows thickenings which are the anlagen of the chorionic villi, surrounded by syncytial trophoderm. In the fourth stage (D), based on Graf Spee's embryo, the chorionic villi are longer and branched. The mesoderm now remains unsplit only at the posterior end of the embryo, where it forms the *body stalk* peculiar to Unguiculates and Primates. It connects the mesoderm of the embryo with the mesoderm of the chorion. Into it there has grown from the gut of the embryo the entodermal diverticulum of the allantois.

The Chorion.—The human chorion is derived directly from the outer trophoblast layer of the blastodermic vesicle and from the extra-embryonic somatic mesoderm. At first, its structure resembles that of the pig's chorion. The trophoblast of the human embryo, however, early gives rise to a thickened outer layer, the *trophoderm* (syncytial and nutrient layer—Figs. 74 *C* and 239). When the developing embryo comes

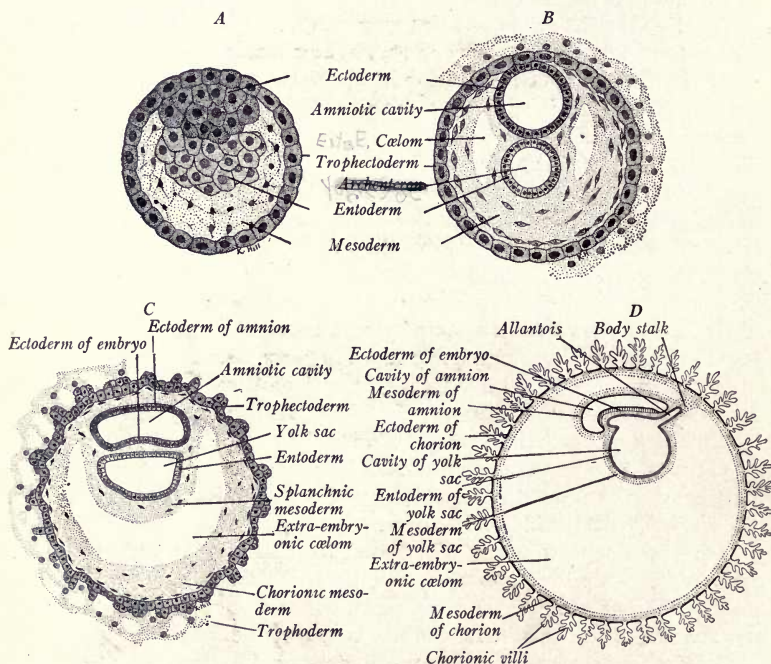


FIG. 74.—Four diagrams of early human embryos (based on figures of Robinson and Minot). *A*, Hypothetical stage; *B*, Bryce-Teacher embryo (modified); *C*, Peters' embryo; *D*, Graf Spee's embryo.

into contact with the uterine wall, the trophoderm destroys the maternal tissues. The destruction of the uterine mucosa serves two purposes: (1) the embedding and attachment of the embryo, it being grafted, so to speak, to the uterine wall; and (2) it supplies the embryo with a new source of nutrition. To obtain nutriment to better advantage, there grow out from the chorion into the uterine mucosa branched processes, or *villi*. The villi are bathed in maternal blood, and in them blood vessels are developed, the trunks of which pass to and from the embryo as the um-

bilical vessels. The embryo receives its nutriment and oxygen, and gets rid of waste products through the walls of the villi. The region where the attachment of the chorionic villi to the uterine wall persists during fetal life is known as the *placenta*. It will be described later with the decidual membranes of the uterus (p. 237 ff.).

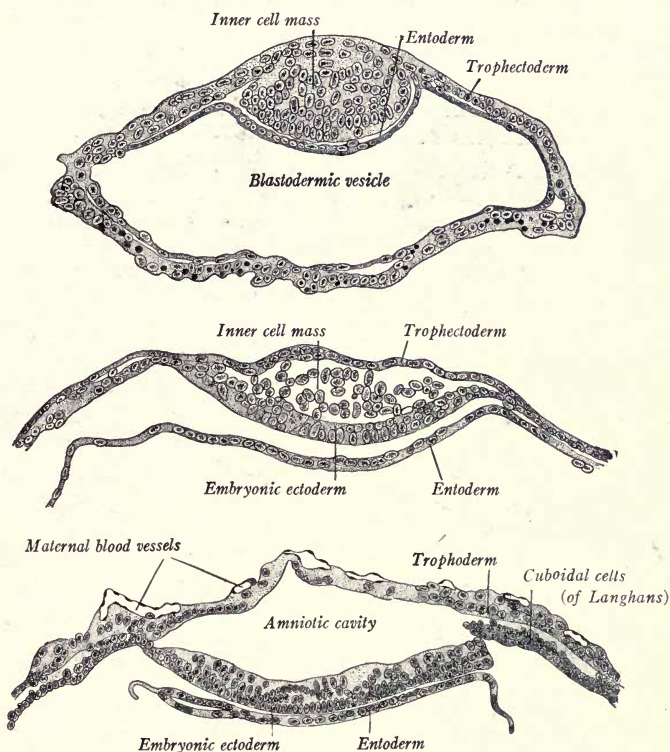


FIG. 75.—Sections showing the formation of the amnion in bat embryos (after Van Beneden).
X about 160.

We saw how the allantois of Ungulates had assumed the nutritive functions performed by the yolk sac in birds, with a consequent degeneration of the ungulate yolk sac. In man and most Unguiculates the functions of the allantois are transferred to the chorion, and the allantois, in turn, becomes a rudimentary structure.

The Amnion.—This is formed precociously in Unguiculates, and in a manner quite different from its mode of origin in Ungulates and birds.

It is assumed that its cavity arises as a split in the primitive ectoderm of human embryos, as in bat embryos (Fig. 75). Later, a somatic layer of mesoderm envelops its ectodermal layer, its component parts then being the same as in birds and Ungulates—an inner layer of ectoderm and an outer layer of mesoderm (Fig. 74 D). It becomes a thin, pellucid, non-vascular membrane, and about a month before birth is in contact with the chorion. It then contains about a liter of amniotic fluid, the origin of which is unknown. During the early months of pregnancy the embryo, suspended by the umbilical cord, floats in the amniotic fluid which serves as a water cushion. The embryo is protected from maceration by a white, fatty secretion, the *vernix caseosa*.

At birth the membranes rupture. If the chorion bursts alone, the child may be born enveloped in the amnion, popularly known as a *veil*, or '*caul*.' The amniotic fluid may be present in excessive amount, the condition being known as *hydramnios*. If less than the normal amount of fluid is present, the amnion may adhere to the embryo and produce malformations. It has been found, too, that fibrous bands or cords of tissue sometimes extend across the amniotic cavity, and, pressing upon parts of the embryo during its growth, cause scars and splitting of eyelids or lips. Such amniotic threads may even amputate a limb or cause the bifurcation of a digit.

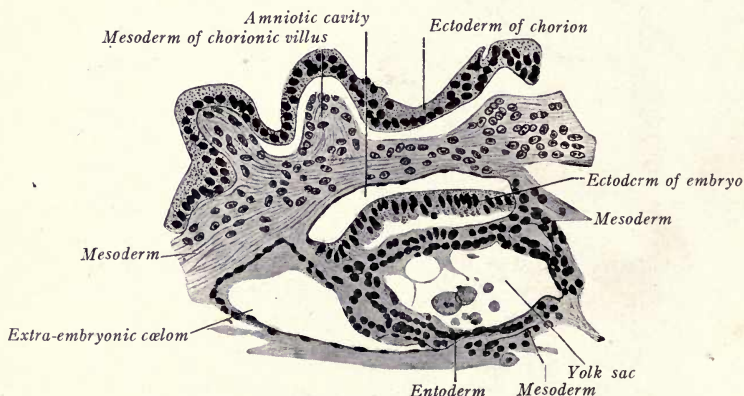


FIG. 76.—Section of Peters' embryo of 0.2 mm. (about fifteen days). The portion of extra-embryonic cœlom shown is limited below by a strand of the magma reticulare.

The Allantois.—The allantois appears very early in the human embryo, before the development of the fore-gut or hind-gut. In Peters' embryo the amnion, chorion, and yolk sac are present, but not the allantois (Fig. 76). In an embryo 1.54 mm. long, described by von Spee (Fig. 77), there is no hind-gut, but the allantoic diverticulum of the en-

totoderm has invaded the mesoderm of the body stalk. This embryo, seen from the dorsal side with the amnion cut away, shows a marked neural

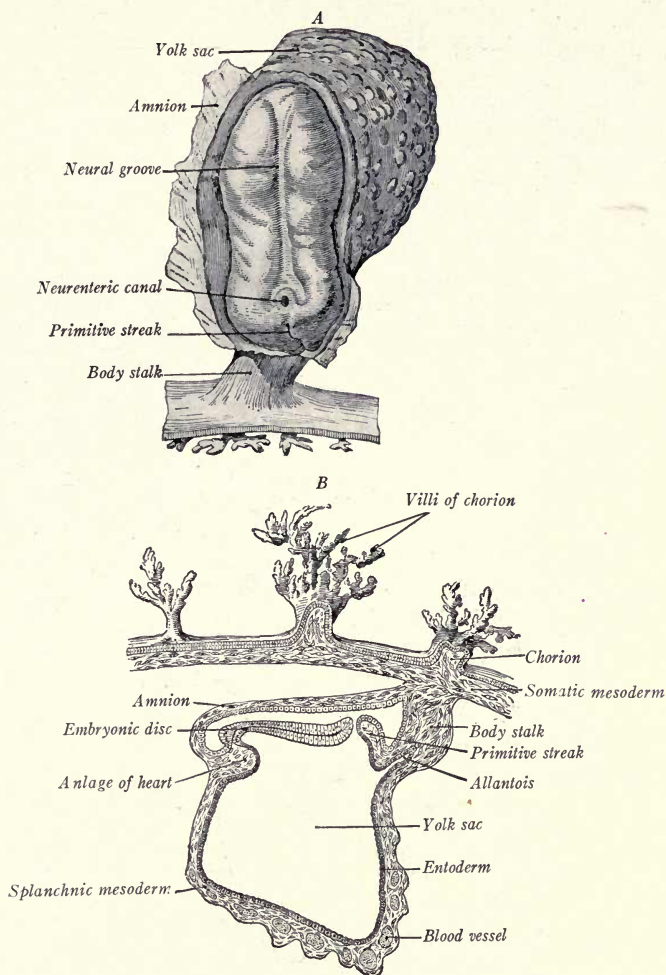


FIG. 77.—Views of a human embryo of 1.54 mm. (von Spee). $\times 23$. A, Dorsal surface; B, median sagittal section.

groove and primitive streak. In front of the primitive knot a pore is figured, leading from the neural groove into the primitive intestinal

cavity, and hence called the *neurenteric canal* (p. 34). The fore-gut and head fold have formed at this stage and there are branched chorionic villi. Somewhat more advanced conditions are found in an embryo of 1.8 mm. with five to six pairs of segments (Fig. 78).

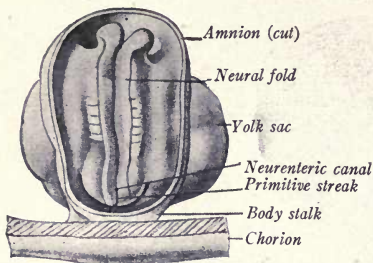


FIG. 78.—Krömer human embryo of 1.8 mm., in dorsal view (after Keibel and Elze). $\times 20$.

A reconstruction by Dandy of Mall's embryo, about 2 mm. long with seven pairs of segments, shows well the embryonic appendages (Fig. 79). The fore- and hind-gut are well developed, the amniotic cavity is large, and the yolk sac still communicates with the gut through a wide opening. The allantois is present

as a curved tube, somewhat dilated near its blind end and embedded in the mesoderm of the body stalk. As the hind-gut develops, the allantois

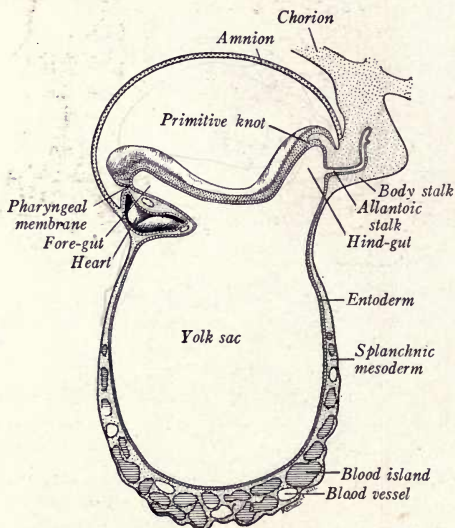


FIG. 79.—A human embryo of 2 mm. in median sagittal section (adapted from reconstructions of Mall's embryo by F. T. Lewis and Dandy). $\times 23$.

comes to open into its ventral wall. A large umbilical artery and vein are present in the body stalk.

In an embryo of 23 somites, 2.5 mm. long, described by Thompson, the allantois has elongated and shows three irregular dilatations (Fig. 80). A large cavity never appears distally in the human allantois as in Ungulates, but when it becomes included in the umbilical cord its distal portion is tubular. The allantois eventually atrophies and is without further significance (cf. p. 209).

The human allantois is thus small and rudimentary as compared with that of birds and Ungulates. As we have seen, the cavity is very large in the pig, and Haller found an allantoic sac two feet long connected with a goat embryo of

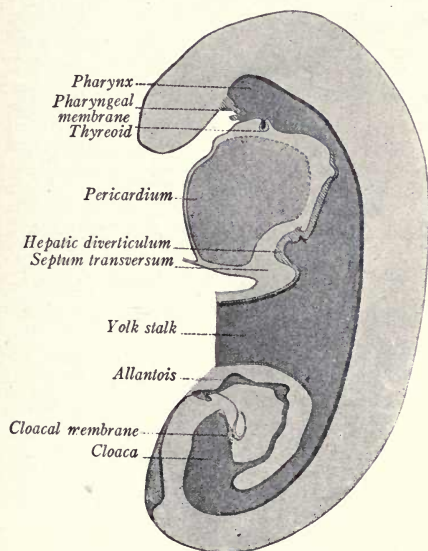


FIG. 80.—Median sagittal section of a 2.5 mm. human embryo, showing digestive tract (after Thompson). $\times 40$.

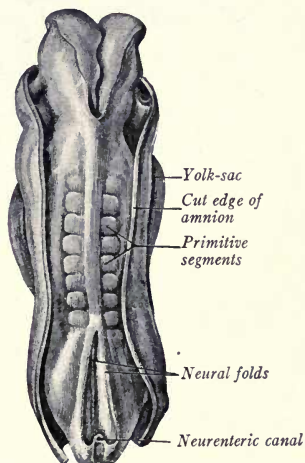


FIG. 81.—Human embryo of 2.11 mm. (Eternod). $\times 35$.

two inches. In human embryos it appears very early and is not free, but embedded in the body stalk. Its functions, so important in birds and Ungulates, are in man performed by the chorion.

The Yolk Sac and Stalk.—In the youngest human embryos described, the entoderm forms a somewhat elongated vesicle (Fig. 76). With the development of the fore-gut and hind-gut in embryos of 1.54 and 2 mm. (Figs. 77 and 79), the entodermal vesicle is divided into the dorsal intestine and ventral *yolk sac*, the two being connected by a somewhat narrower region. This condition persists in an embryo 2.5 mm. long (Fig. 80). In the figure, most of the yolk sac has been cut away. Embryos with

9 and 14 pairs of segments, with three brain vesicles and with the amnion cut away are seen in Figs. 81 and 324. The relation of the fetal appen-

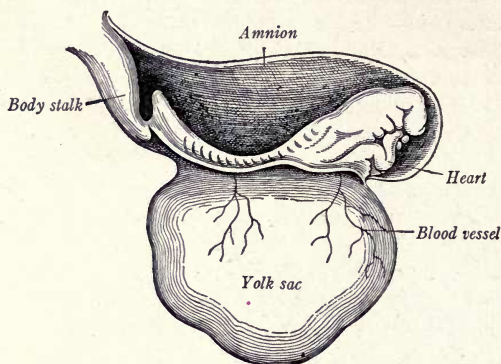


FIG. 82.—Human embryo of about 2.5 mm. (His, after Coste). $\times 15$.

dages to the embryo shows well in the embryo of Coste (Fig. 82). The dorsal concavity is probably abnormal. A robust body stalk attaches the

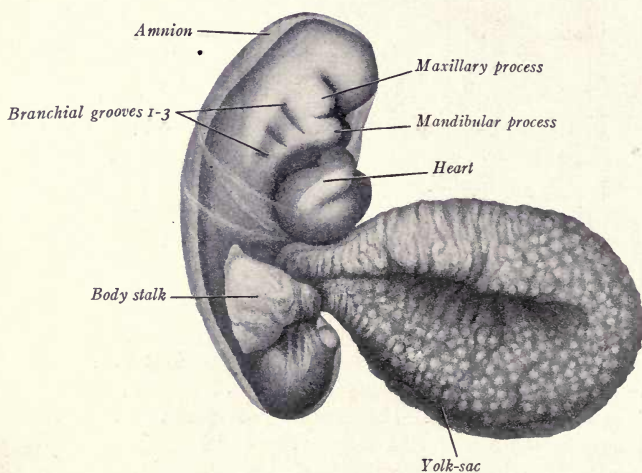


FIG. 83.—Human embryo of 2.6 mm., showing amnion, yolk stalk and body stalk (His). $\times 25$.

embryo to the inner wall of the chorion. With the growth of the head- and tail folds of the embryo, there is an apparent constriction of the yolk

sac where it joins the embryo. This, however, is a deception. Both embryo and yolk sac enlarge, whereas the region of union lags and later becomes the slender *yolk stalk* (Fig. 84). His' embryo, 2.6 mm. long, shows the relative size of yolk sac and embryo and the yolk stalk (Fig. 83). The relations of the fetal membranes to the embryo are much the same as in the chick embryo of five days, save that the allantois of the human embryo is embedded in the body stalk. The embryo shows a regular, convex dorsal curvature, there is a marked cephalic bend in the region of the mid-brain and there are three branchial grooves. The head is twisted to the left, the tail to the right. At the side of the oral sinus are two large processes; the dorsal of these is the *maxillary*, the ventral the *mandibular process*. The heart is large and flexed in much the same way as the heart of the fifty-hour chick embryo.

In later stages, with the development of the umbilical cord, the yolk stalk becomes a slender thread extending from the dividing line



FIG. 84.—Yolk sac and stalk of a 20 mm. human embryo. $\times 11$.

between the fore- and hind-gut to the yolk sac, or umbilical vesicle (Figs. 84 and 119). It loses its attachment to the gut in 7 mm. embryos. A blind pocket may persist at its point of union with the intestine; this is known as *Meckel's diverticulum*, a structure of clinical importance because it sometimes telescopes and causes the occlusion of the intestinal lumen. The yolk stalk may remain embedded in the umbilical cord and extend some distance to the yolk sac which is found between the amnion and chorion. The yolk sac may be persistent at birth.

THE ANATOMY OF A 4.2 MM. HUMAN EMBRYO

This embryo, studied and described by His, is regarded by Keibel as not quite normal. Viewed from the left side (Fig. 85), with the amnion cut away close to its line of attachment, there may be seen the yolk stalk, and a portion of the yolk sac and body stalk. There is an indication of the primitive segments along the dorso-lateral line of the trunk. The head is bent ventrad almost at right angles, forming in the mid-brain region the *cephalic flexure*. There are also marked cervical and caudal flexures, the trunk ending in a short, blunt tail. The heart is large and

flexed as in the earlier stage. Three branchial grooves separate the four branchial arches. The first arch has developed two ventral processes. Of these, the *maxillary process* is small and may be seen dorsal to the *stomodæum*. The *mandibular process* is large and has met its fellow of the right side to form the mandible, or lower jaw. Dorsal to the second branchial groove may be seen the position of the oval *otocyst*, now a closed

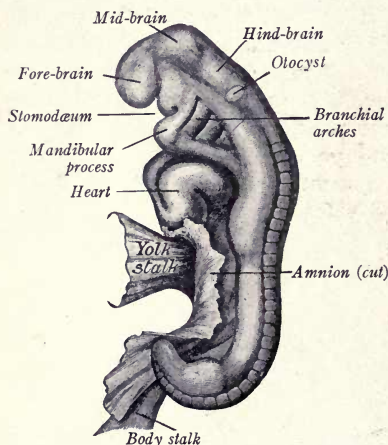


FIG. 85.—Human embryo of 4.2 mm., in lateral view (His). $\times 15$.

sac. Opposite the atrial portion of the heart, and in the region of the caudal flexure, bud-like outgrowths indicate the anlagen of the upper and lower extremities.

Central Nervous System and Sense Organs. The neural tube is closed throughout its extent and is differentiated into brain and spinal cord. The brain tube, or *encephalon*, is divided by constrictions into four regions, or vesicles, as in the fifty-hour chick (Fig. 57). Of these, the most cephalad is the *telencephalon*. It is a paired outgrowth from the fore-brain, the remaining portion of which is the *diencephalon*. The mid-brain, or *mesencephalon*, located at the cephalic flexure, is

not subdivided. The hind-brain, or *rhombencephalon*, which is long and continuous with the spinal cord, later is subdivided into the *metencephalon* (region of the cerebellum and pons) and *myelencephalon* (medulla oblongata). The spinal cord forms a closed tube extending from the brain to the tail and containing the neural cavity, flattened from side to side.

The *eye* is represented by the optic vesicles and the thickened ectodermal anlage of the lens. Its stage of development is between that of the thirty-eight- and fifty-hour chick embryos.

The *otocyst* is a closed sac, no longer connected with the outer ectoderm as in the fifty-hour chick.

Digestive Canal.—In a reconstruction of the viscera viewed from the right side (Fig. 86), the entire extent of the digestive canal may be seen. The *pharyngeal membrane*, which we saw developed in the chick between the stomodæum and the pharynx, has broken through so that these cavities are now in communication. The *fore-gut*, which extends from the oral

cavity to the yolk stalk, is differentiated into pharynx, thyreoid, trachea and lungs, esophagus and stomach, small intestine and digestive glands (pancreas and liver). The gut is suspended from the dorsal body wall by the *dorsal mesentery*.

The ectodermal limits of the oral cavity are indicated dorsad by the diverticulum of the hypophysis (*Rathke's pouch*). The fore-gut proper

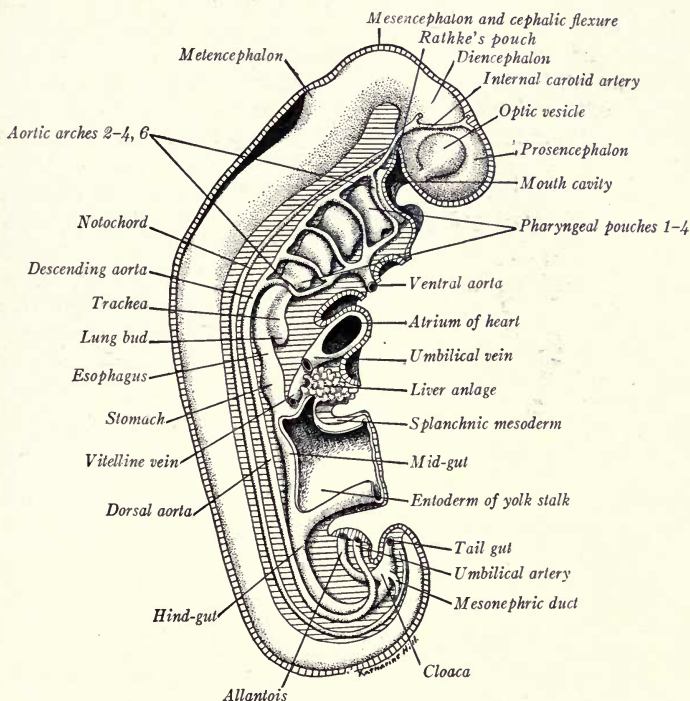


FIG. 86.—Diagrammatic reconstruction of a 4.2 mm. human embryo, viewed from the right side (adapted from a model by His). $\times 25$.

begins with a shallow out-pocketing known as *Seessel's pouch*. As the pharyngeal membrane disappears between these pockets, it would seem that Seessel's pouch represents the persistence of the blind anterior end of the fore-gut. No other significance has been assigned to it.

The *pharynx* is widened laterally, and at this stage shows four *pharyngeal pouches* (Fig. 87). Later a fifth pair of pouches is developed (Fig. 168). The four pairs of pharyngeal pouches are important as they

form respectively the following adult structures: (1) the *auditory tubes*; (2) the *palatine tonsils*; (3) the *thymus* and *parathyroids*; (4) the *parathyroids*. Between the pharyngeal pouches are the five branchial arches in which are developed five pairs of aortic arches. Between the bases of the first and second branchial arches, on the floor of the pharynx, is developed the transient *tuberculum impar*. Posterior to this unpaired structure there grows out ventrally the anlage of the *thyroid gland*. From

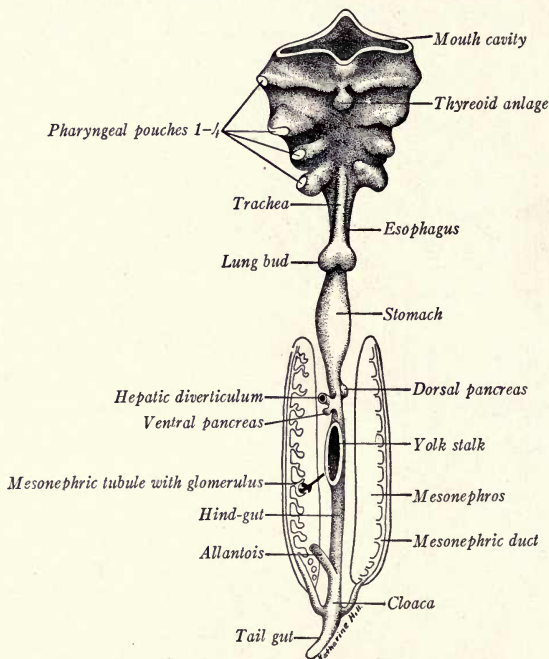
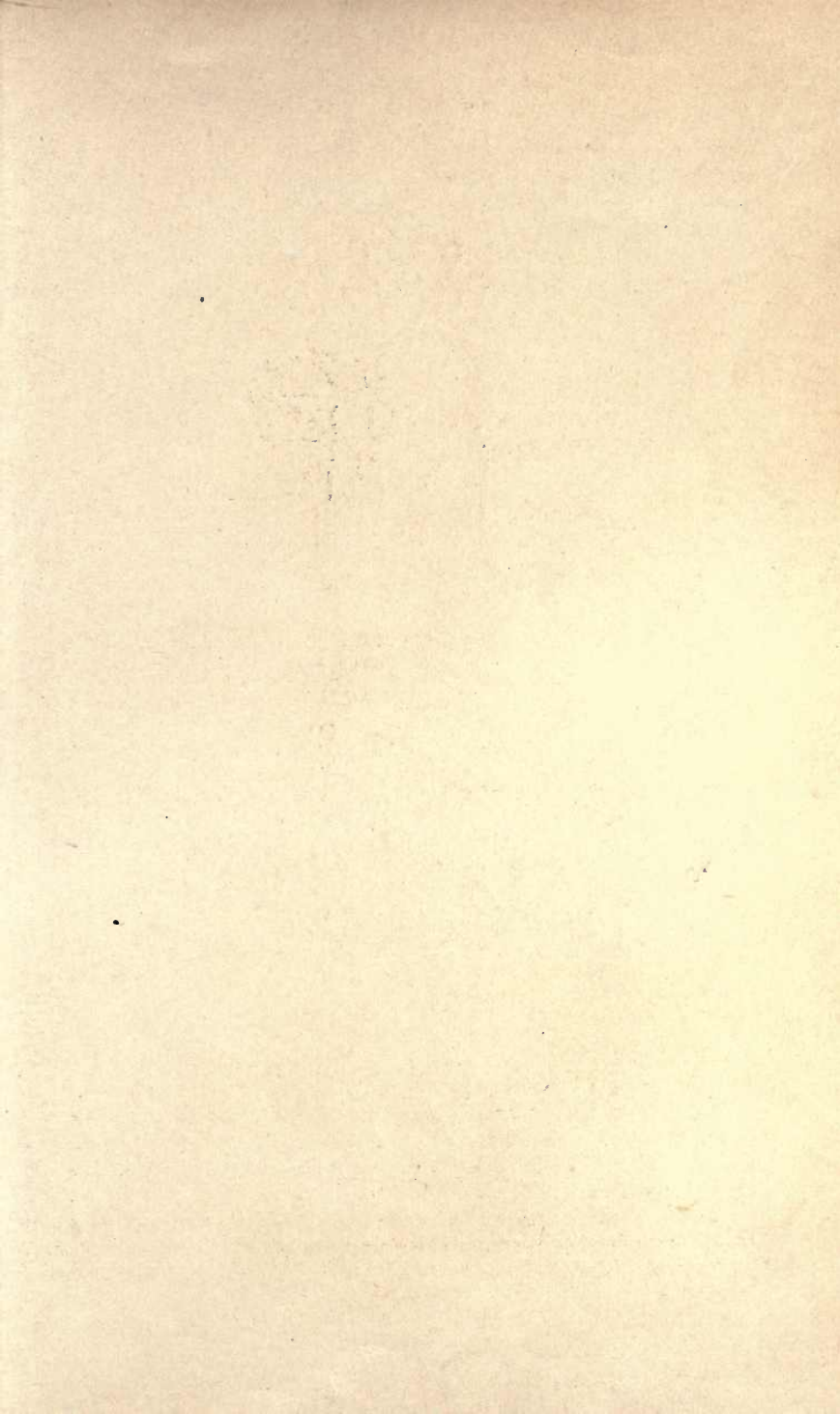


FIG. 87.—Diagrammatic ventral view of pharynx, digestive tube, and mesonephroi of a 4-5 mm. embryo (based on reconstructions by Grosser and His). \times about 30. The liver and yolk sac are cut away. The tubules of the right mesonephros are shown diagrammatically.

the caudal end of the trachea have appeared ventrally the *lung buds*. The trachea is still largely a groove in the ventral wall of the pharynx and esophagus (Fig. 86). Caudal to the lungs, a slight dilation of the digestive tube indicates the position of the *stomach*. The *liver diverticulum* has grown out from the fore-gut into the ventral mesentery, cranial to the wall of the yolk stalk. It is much larger than in the fifty-hour chick, where its paired anlage was seen cranial to the intestinal portal, and is separated from the heart by the *septum transversum*. The small intestine between the liver and yolk stalk is short and broad. In later stages it



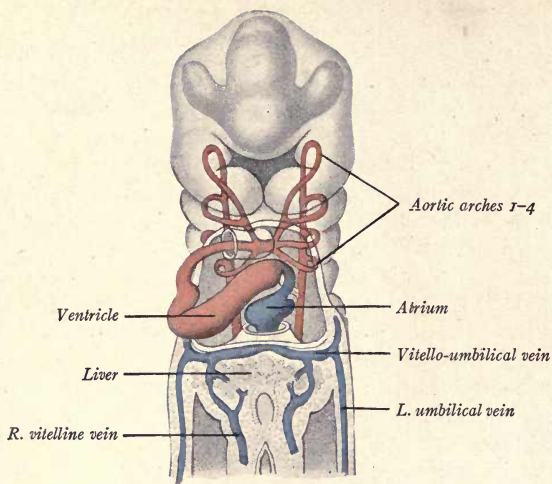


FIG. 88.—Ventral reconstruction of a 3.2 mm. embryo, showing vessels (His).

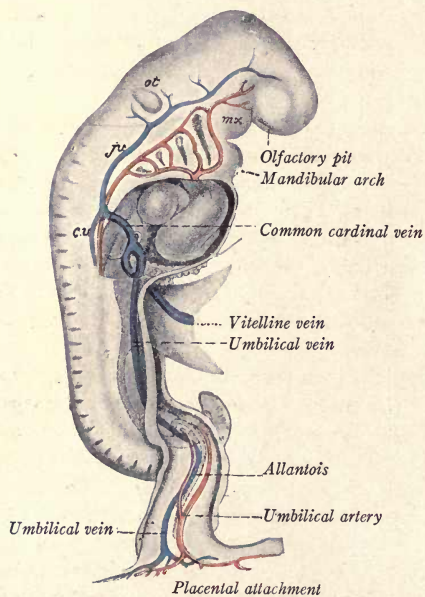


FIG. 89.—Lateral view of human embryo of 4.2 mm., showing aortic arches and venous trunks (His).
mx, Maxillary process; *ju*, anterior cardinal vein; *cv*, posterior cardinal vein; *ot*, otocyst.

becomes enormously elongated as compared with the rest of the digestive tube. The yolk stalk is still expansive. The region of its attachment to the gut corresponds to the open mid-gut of the chick embryo. The *hind-gut* and tail fold of this embryo are greatly elongated as compared with the chick embryo of fifty hours. The hind-gut terminates blindly in the tail. Near its caudal end it is dilated to form the *cloaca*. Into the ventral side of the cloaca opens the stalk of the *allantois*. Dorso-laterally the primary excretory (Wolffian) ducts which we saw developed in the fifty-hour chick have connected with the cloaca and open into it. Caudal to the cloaca, on the ventral side, is the *cloacal membrane*, which later divides and breaks through to form the genital aperture and anus. That part of the hind-gut between the cloaca and the yolk stalk forms the rectum, colon, cæcum, and appendix, together with a portion of the small intestine (ileum).

Urogenital Organs.—The opening of the primary excretory (Wolffian) ducts into the cloaca has been noted. These are the ducts of the mid-kidney, or *mesonephros*. At this stage, the nephrotomes, which in the chick embryos were seen to form the anlagen of these ducts, are also forming the kidney tubules of the mesonephros which open into the ducts (Fig. 87). The mid-kidneys project into the peritoneal cavity as ridges on each side. A thickening of the mesothelium along the median halves of the mesonephroi forms the anlagen of the genital glands, or *gonads* (Fig. 220).

Circulatory System.—The *heart* is an S-shaped double tube as in the fifty-hour chick. The outer myocardium is confined to the heart while the inner endothelial layer is continuous, at one end with the veins, at the other end with the arteries. The disposition of the heart tube is well seen in a ventral view of a younger embryo (Fig. 88). The veins enter the sinus venosus just cranial to the yolk sac. Next in front is the *atrium*, with the convexity of its flexure directed cephalad. The ventricular portion of the heart is U-shaped and is flexed to the right of the embryo. The left limb is the *ventricle*, the right the *bulbus*.

The *arteries* begin with the *ventral aorta* which bends back to the mid-plane and divides into five branches on each side of the pharynx (Figs. 88 and 89). These are the *aortic arches* and they unite dorsally to form two trunks, the *descending aortæ*. The aortic arches pass around the pharynx between the pharyngeal pouches in the branchial arches. The arrangement is like that of the adult fish which has gill slits, branchial arches, and aortic arches to supply the gills. The descending aortæ run caudal, and, opposite the lung buds, unite to form a single, median *dorsal aorta*. This, in the region of the posterior limb buds, divides into the two *umbilical arteries*, which, curving cephalad and ventrad, enter the body stalk on each side of

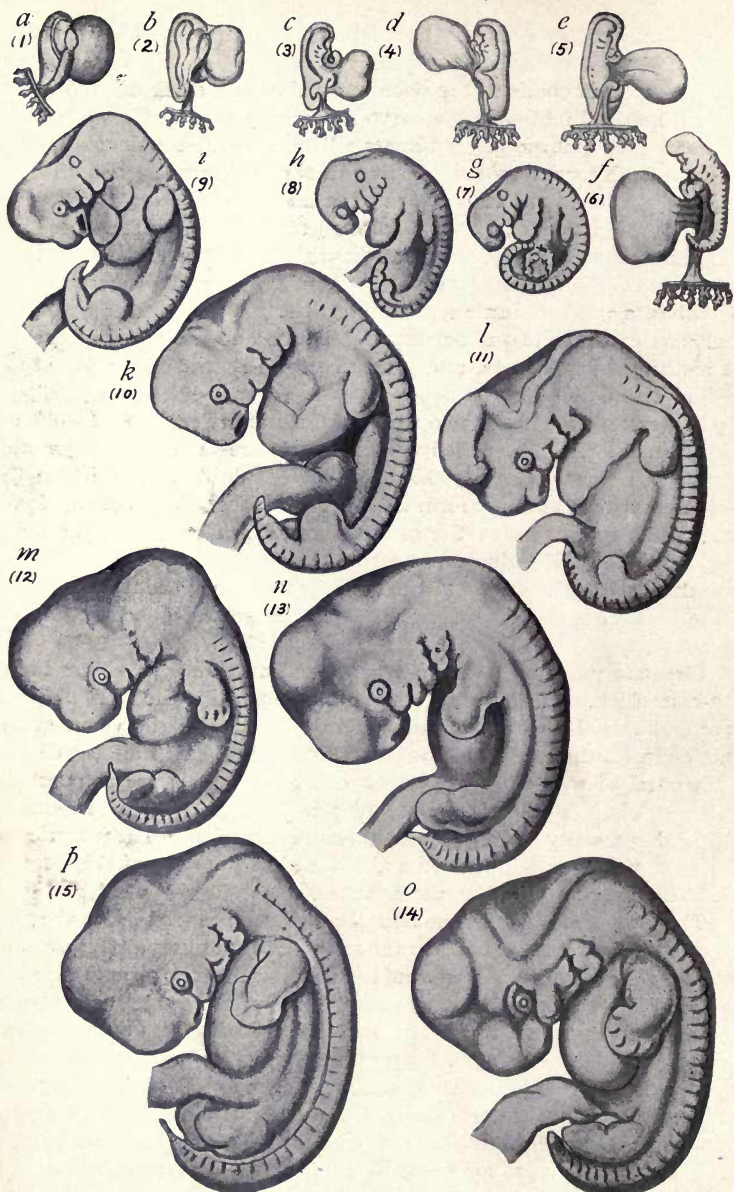


FIG. 90.—Embryos of four to six weeks (2.1 to 11 mm.). From His' Normentafel (Keibel and Elze). $\times 5$.

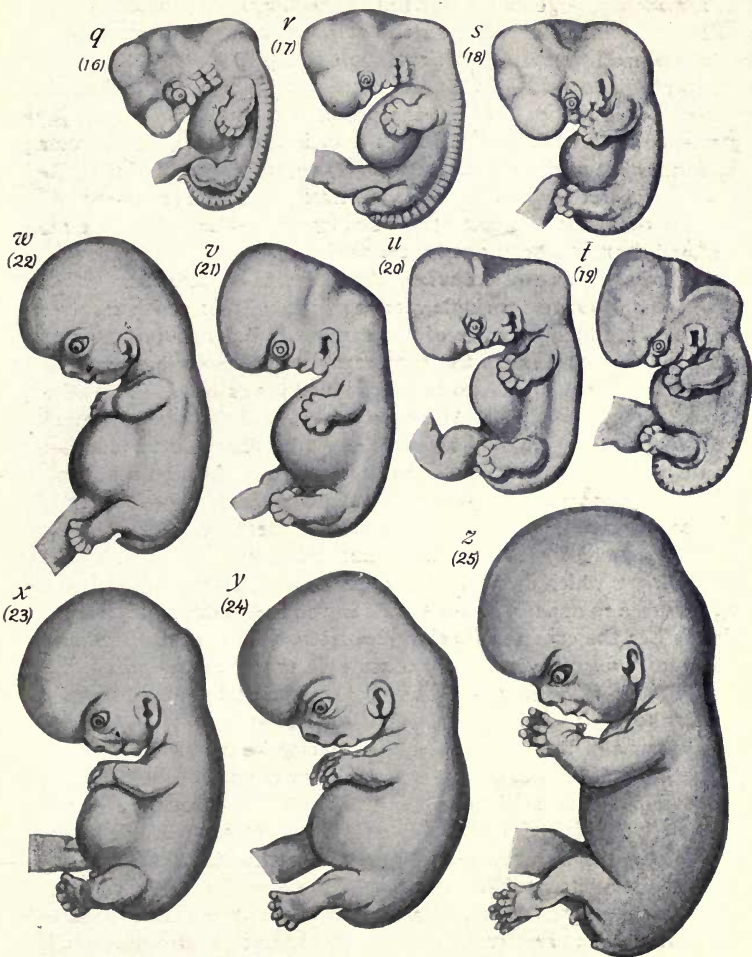


FIG. 91.—Embryos of six to eight weeks (12.5 to 23 mm.). From His' Normentafel (Keibel and Elze). $\times 2.5$. Stage *w*(22) marks the transition from embryo to fetus.

the allantois and eventually ramify in the villi of the chorion. The *vitelline arteries*, large and paired in the chick, are represented by a single, small trunk which branches on the surface of the yolk sac (Fig. 271). Compared with the arterial circulation of the chick of fifty hours the important differences are: (1) the development of the fourth and fifth pairs of aortic arches, and (2) the presence of the chorionic circulation, by way of the umbilical arteries, in addition to the vitelline circulation found in the fifty-hour chick.

The *veins* are all paired and symmetrically arranged (Figs. 88 and 279). There are three sets of them: (1) The blood from the body of the embryo is drained, from the head end by the *anterior cardinal veins*, from the tail end by the *posterior cardinal veins*. These veins on each side unite dorsal to the heart and form a single *common cardinal vein* which receives the vitelline and umbilical veins of the same side before joining the heart. (2) Paired *vitelline veins* in the early stages of the embryo drain from the yolk sac the blood carried to it by the vitelline arteries. The trunks of these veins pass back into the body on each side of the yolk stalk and liver, and, with the paired umbilical veins, form a trunk that empties into the sinus venosus of the heart. As the liver develops, it may be seen that the vitelline veins break up into blood spaces, called *sinusoids* (Fig. 279). When the liver becomes large and the yolk sac rudimentary, the vitelline veins receive blood chiefly from the liver and intestine. (3) A pair of large *umbilical veins* which drain the blood from the villi of the chorion and are the first veins to appear. These unite in the body stalk, and, again separating, enter the somatopleure on each side. They run cephalad to the septum transversum where they unite with the vitelline veins to form a common *vitello-umbilical* trunk which joins the common cardinal and empties into the sinus venosus.

The veins of this embryo are thus like those of the fifty-hour chick save that *the umbilical vessels are now present and take the place of the allantoic veins of later chick embryos*. The veins, like the heart and arteries, are primitively paired and symmetrically arranged. As development proceeds, their symmetry is largely lost and the asymmetrical venous system of the adult results.

The later stages of the human embryo cannot be described in detail here. The student is referred to the texts of Minot, and Keibel and Mall. Figs. 90 and 91 show a series of human embryos described by His, the ages of which lie between four and eight weeks. The figures show as well as could any description the changes which lead toward the adult form when the embryo may be called a *fetus* (stage *w*). The external metamorphosis is due principally: (1) to changes in the flexures of the

embryo; (2) to the development of the face; (3) to the development of the external structure of the sense organs (nose, eye, and ear); (4) to the development of the extremities and disappearance of the tail. The more important of these changes will be dealt with in later chapters.

THE AGE OF HUMAN EMBRYOS

The ages of the human embryos which have been obtained and described cannot be determined with certainty, because too little is known of the time relations between ovulation, coitus, and fertilization. Furthermore, ovulation need not bear a definite relation to menstruation (p. 11). This lack of a reliable basis makes any computation only approximate.

In 1868, Reichert, from studying the corpus luteum in ovaries obtained during menstruation, concluded that ovulation takes place as a rule just before menstruation, and that if the ovum is fertilized the approaching menstruation does not occur. Reichert then decided that a human embryo of 5.5 mm., which he had obtained from a woman two weeks after menstruation failed to occur, must be two weeks, not six weeks, old. His accepted Reichert's views and the ages of embryos were for a long time estimated on this basis. According to this method, Peters' ovum, obtained thirty days after the last period, is only three or four days old. This, however, does not agree at all with the known ages of other mammalian embryos equally developed.

From numerous clinical observations we must conclude that ovulation does not immediately precede menstruation, but that most pregnancies follow a coitus within a week or ten days after the menses cease. *It is therefore more correct to compute the age of an embryo from the tenth day after the onset of the last menstruation.* To compare an embryo with one of known age, the *crown-rump length* (that is, from vertex to breech) is usually taken. Young embryos vary greatly in size so their structure must be taken into account as well.

Of practical interest is the determination of the date of delivery of a pregnant woman. Most labors occur ten lunar months, or 280 days, from the first day of the last menstrual period. The month and day of this date are easily found by counting back three months from the first day of the last period, and then adding six days. As some women menstruate once or more after becoming pregnant this computation is not infallible.

The following are the estimated ages and lengths of human embryos, according to Mall, and their weights according to Jackson.

Age	Crown-rump length (CR), or sitting height (mm.).	Crown-heel length (CH), or standing height (mm.).	Weight in grams
Twenty-one days.....	0.5	0.5	
Twenty-eight days.....	2.5	2.5	
Thirty-five days.....	5.5	5.5	.04
Forty-two days.....	11.0	11.0	
Forty-nine days.....	17.0	19.0	
Second lunar month.....	25.0	30.0	3
Third lunar month.....	68.0	98.0	36
Fourth lunar month.....	121.0	180.0	120
Fifth lunar month.....	167.0	250.0	330
Sixth lunar month.....	210.0	315.0	635
Seventh lunar month.....	245.0	370.0	1220
Eighth lunar month.....	284.0	425.0	1700
Ninth lunar month.....	316.0	470.0	2240
Tenth lunar month.....	345.0	500.0	3200

For comparison and reference the gestation periods of a few representative mammals are appended:

Opossum..... 13 days	Pig..... 17 weeks
Mouse..... 20 days	Sheep..... 21 weeks
Rat..... 21 days	Cow..... 41 weeks
Rabbit..... 30 days	Horse..... 48 weeks
Cat..... 8 weeks	Rhinoceros..... 18 months
Dog, guinea pig..... 9 weeks	Elephant..... 20 months

CHAPTER V

THE STUDY OF SIX AND TEN MILLIMETER PIG EMBRYOS

A. THE ANATOMY OF A SIX MM. PIG EMBRYO

VERY young pig embryos of the primitive streak and neural fold stages have been seen already (Fig. 26). In its early stages the pig embryo is flattened out on the surface of the yolk sac like a chick embryo (Fig. 92), but as the head and tail folds elongate, the body becomes flexed and twisted spirally, making it difficult to study. In embryos 5 to 7 mm. long, the twist of the body begins to disappear and its structure may be seen to better advantage. The anatomy of a 7.8 mm. pig embryo has been studied by Thyng (*Anat. Record*, vol. 5, 1911).

External Form of 6 mm.

Embryo.—When compared with the form of the 4 mm. human embryo, the marked difference in a 6 mm. pig is the convex dorsal flexure which brings the head and tail regions close together (Fig. 93). The *cephalic flexure* at the mesencephalon forms an acute angle and there is a marked neck, or *cervical flexure*. As a result, the head is somewhat triangular in form. The body is bent dorsad in an even, convex curve and the tail

is flexed sharply dorsad. Lateral to the dorsal line may be seen the segments, which become larger and more differentiated from tail to head. At the tip of the head a shallow depression marks the anlage of the *olfactory pit*. The *lens vesicle* of the eye is open to the exterior. Caudal to the eyes, at the sides of the head, are four *branchial arches* separated by three *branchial grooves*. The fourth arch is partly concealed in a triangular depression, the *cervical sinus*,

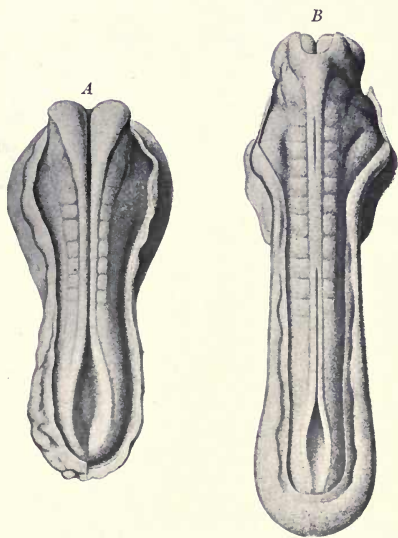


FIG. 92.—Pig embryos, (A) of seven and (B) of eleven primitive segments, in dorsal view with amnion cut away (Keibel, Normmentafel). $\times 20$.

formed by the more rapid growth of the first and second arches (cf. Fig. 97). The first, or *mandibular arch*, forks ventrally into two processes, a smaller *maxillary* and a larger *mandibular process*, and the latter with its fellow forms the mandible or lower jaw. The position of the mouth is indicated by the cleft between these processes. The groove between the eye and the mouth is the *lacrimal groove*.

The second, or *hyoid arch* is separated from the mandibular arch by a *hyomandibular cleft* which persists as the *external auditory meatus*. About the dorsal end of the cleft develops the external ear.

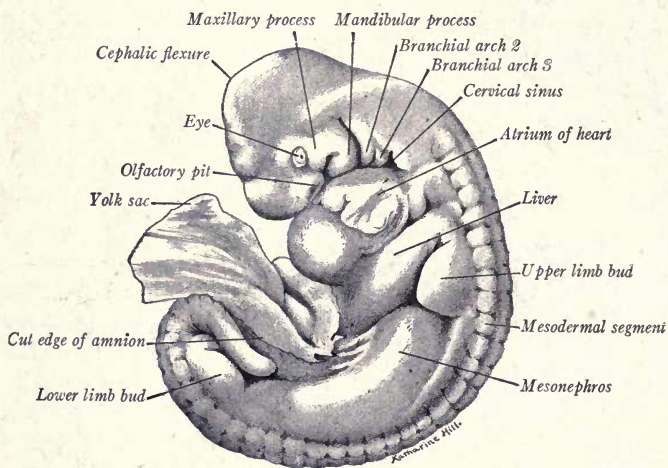


FIG. 93.—Pig embryo of 6 mm., viewed from the left side. The amnion has been removed.
× 12.

The heart is large, and through the transparent body wall may be seen the dorsal *atrium* and ventral *ventricle*. Caudal to the heart a convexity indicates the position of the *liver*. Dorsal to the liver is the bud of the upper limb, now larger than in the 4 mm. human embryo. Extending caudal to the anlage of the upper extremity, a curved convexity indicates the position of the left *mesonephros*. At its caudal end is the bud of the *lower limb*. The amnion has been dissected away along the line of its attachment, ventral to the mesonephros. There is as yet no distinct umbilical cord and a portion of the body stalk is attached to the embryo.

Due to a shorter term of development, a young pig embryo is somewhat precociously developed in comparison with a human embryo of the same size (Fig. 94). In a human embryo 7 mm. long the head is larger,

the tail shorter. The cervical flexure is more marked, the olfactory pits larger and deeper. The liver is more prominent than in the 6 mm. pig, the mesonephros and segments less so.

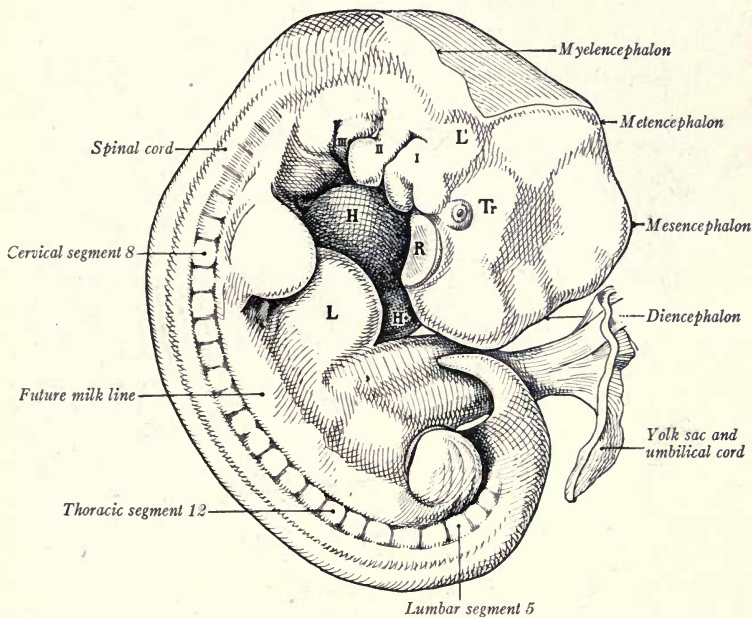


FIG. 94.—A human embryo 7 mm. long, viewed from the right side (Mall in Kollmann). $\times 14$. *I, II, III*, Branchial arches 1, 2, and 3; *H, Hl*, heart; *L*, liver; *L'*, otic vesicle; *R*, olfactory placode; *Tr*, semilunar ganglion of trigeminal nerve.

DISSECTIONS OF THE VISCERA

To understand the sectional anatomy of an embryo, a study of dissections and reconstructions is essential. For methods of dissection see p. 139, Chapter VI. Before studying sections, the student should become as well acquainted as possible with the anatomy of the embryo and compare each section with the figures of reconstructions and dissections.

Nervous System.—Fig. 95 shows the central nervous system and viscera exposed on the right side of a 5.5 mm. embryo. The ventro-lateral wall of the head has been left intact, together with the lens cavity, olfactory pit, and portions of the maxillary and mandibular processes, second and third branchial arches, and cervical sinus (cf. Fig. 93). The brain is differentiated into the five regions: *telencephalon*, *diencephalon*,

mesencephalon, *metencephalon*, and *myelencephalon*. The spinal cord is cylindrical and gradually tapers off to the tail. The anlagen of the cerebral and spinal ganglia and the main nerve trunks are shown. The *oculomotor nerve* begins to appear from the ventral wall of the *mesencephalon*. Ventro-lateral to the *metencephalon* and *myelencephalon* occur

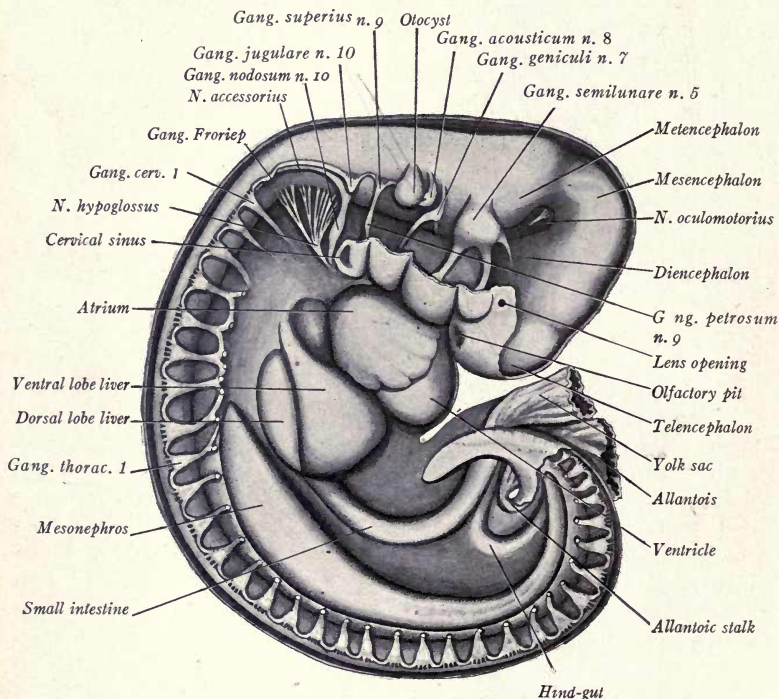


FIG. 95.—Dissection of a 5.5 mm. pig embryo, showing the nervous system and viscera from the right side. $\times 18$.

in order: the *semilunar ganglion* and three branches of the *trigeminal nerve*; the *geniculate ganglion* and nerve trunk of the *n. facialis*; the ganglionic anlage of the *n. acusticus* and the *otocyst*. It will be observed that the nerve trunks are arranged with reference to the branchial arches and clefts. Caudal to the *otocyst* a continuous chain of cells extends lateral to the neural tube into the tail region. Cellular enlargements along this *neural crest* represent developing cerebral and spinal ganglia. They are in order the *superior*, or root ganglion of the *glossopharyngeal nerve* with its distal *petrosal ganglion*; the *ganglion jugulare* and distal

ganglion nodosum of the *vagus nerve*; the ganglionic crest and the proximal portion of the *spinal accessory nerve*; and the anlage of *Froriep's ganglion*, an enlargement on the neural crest just cranial to the first cervical ganglion. Between the *vagus* and *Froriep's ganglion* may be seen the numerous root fascicles of the *hypoglossal nerve*, which take their origin along the ventro-lateral wall of the myelencephalon and unite to form a single trunk. The posterior roots of the spinal ganglia are very short; their anterior, or ventral roots are not shown.

The position of the heart with its *ventricle*, *atrium*, and *sinus venosus* is shown. The *liver* is divided into a small dorsal and a large ventral lobe. The *fore-gut* emerges from between the liver lobes and curves ventrad to the yolk stalk and sac. The *hind-gut* is partly hidden by the *fore-gut*; it makes a U-shaped bend from the yolk stalk to the caudal region. The gut is attached to the dorsal body wall by a double layer of splanchnic mesoderm which forms the *mesentery*. The long, slender *mesonephros* lies ventral to the spinal cord and curves caudad from a point opposite the eighth cervical ganglion to the tail region. The cranial third of the *mesonephros* is widest and its size diminishes tailwards. Between the yolk sac and the tail the allantois is seen, its stalk curving around from the ventral side of the tail region.

Digestive Canal.—The arrangement of the viscera may be seen in median sagittal and ventral dissections (Figs. 96 and 97), and also in the reconstruction shown in Fig. 105. The *mouth* lies between the mandible, the median frontonasal process of the head, and the maxillary processes at the sides. The diverticulum of the hypophysis (*Rathke's pouch*), flattened cephalo-caudad and expanded laterad, extends along the ventral wall of the fore-brain (Fig. 105). Near its distal end, the wall of the brain is thickened and later the posterior lobe of the hypophysis will develop from the brain wall at this point.

The *pharynx* is flattened dorso-ventrally and is widest near the mouth. Its lateral dimension narrows caudad, and opposite the third branchial arch it makes an abrupt bend, a bend which corresponds to the cervical flexure of the embryo's body (Figs. 104 and 105). In the roof of the pharynx, just caudal to *Rathke's pouch*, is the somewhat cone-shaped pouch known as *Seessel's pouch*, which may be interpreted as the blind, cephalic end of the fore-gut. The lateral and ventral walls of the pharynx and oral cavity are shown in Fig. 98. Of the four arches the mandibular is the largest and a groove partly separates the processes of the two sides. Posterior to this groove and extending in the median plane to the hyoid arch is a triangular elevation, the *tuberculum impar*; it later vanishes, apparently contributing nothing to the tongue. At an earlier stage the median *thyroid* anlage grows out from the mid-ventral wall of the pharynx

just caudal to the tuberculum impar. The ventral ends of the second arches fuse in the mid-ventral plane and form a prominence, the *copula*. This connects the tuberculum impar with a rounded tubercle derived from the third and fourth pairs of arches, the anlage of the *epiglottis*. Its cephalic portion forms the root of the tongue (Fig. 156). Caudal to the

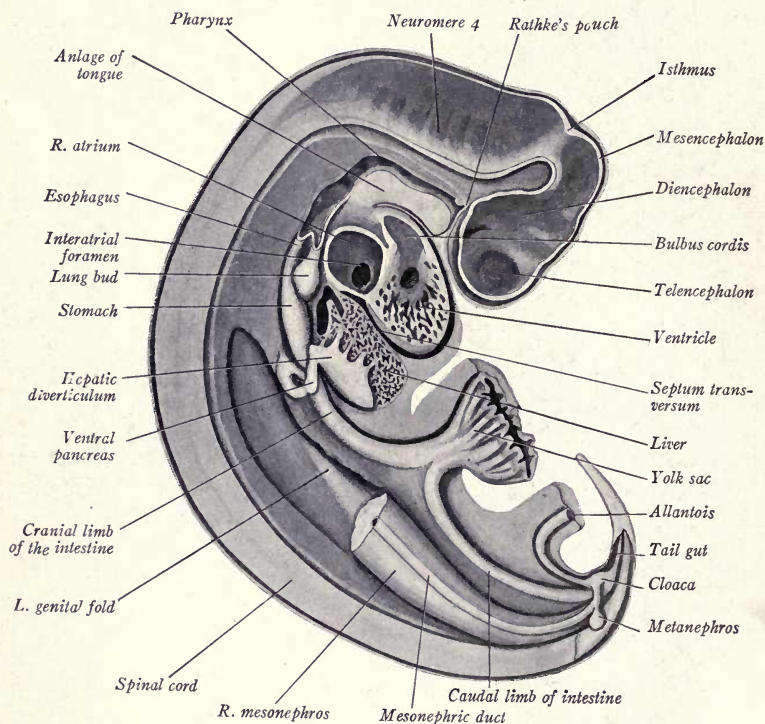


FIG. 96.—Median sagittal dissection of a pig embryo of 6 mm., showing viscera and neural tube. $\times 18$.

epiglottis are the *arytenoid ridges*, and a slit between them, the *glottis*, leads into the trachea.

The branchial arches converge caudad and the pharynx narrows rapidly before it is differentiated into the trachea and esophagus (Figs. 104 and 105). Laterally and ventrally between the arches are the four paired outpocketings of the *pharyngeal pouches*. The pouches have each a dorsal and ventral diverticulum. The dorsal diverticula are large and wing-like (Fig. 104); they meet the ectoderm of the gill clefts and fuse

with it to form the *closing plates*. Between the ventral diverticula of the third pair of pouches lies the median *thyroid anlage*. The fourth pouch is smaller than the others. Its dorsal diverticulum just meets the ectoderm; its ventral portion is small, tubular in form, and is directed parallel to the esophagus (Fig. 104).

The groove on the floor of the pharynx caudal to the epiglottis is continuous with the tracheal groove. More caudally, opposite the atrium

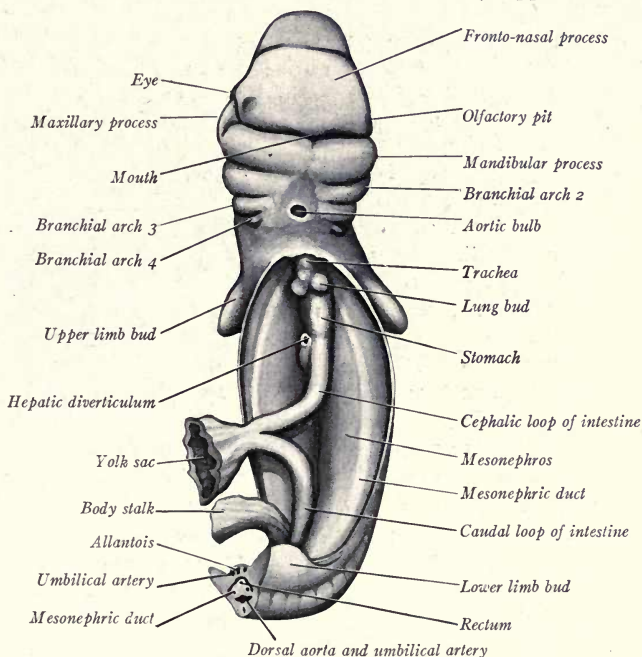


FIG. 97.—Ventral dissection of a 6 mm. pig embryo. The head has been bent dorsally. $\times 14$.

of the heart, the *trachea* has separated from the *esophagus* (Fig. 96). The trachea at once bifurcates to form the *primary bronchi* and the anlagen of the *lungs* (Fig. 97). The lungs consist merely of the dilated ends of the bronchi surrounded by a layer of splanchnic mesoderm. They bud out laterally on each side of the esophagus near the cardiac end of the stomach, and project into the *pleural cælom*. The esophagus is short and widens dorso-ventrally to form the *stomach*. The long axis of the stomach is nearly straight, but its entodermal walls are flattened together and it has revolved on its long axis so that its dorsal border lies to the left, its ventral border to the right, as seen in transverse section (Fig. 111).

Caudal to the pyloric end of the stomach, and to its right, is given off from the duodenum the *hepatic diverticulum*. Its opening into the gut is seen in the ventral dissection (Fig. 97). The hepatic diverticulum is a sac of elongated oval form from which the liver and part of the pancreas take origin, and which later gives rise to the gall bladder, cystic duct, and common bile duct. It is connected by several cords of cells with the trabeculae of the liver.

The *liver* is divided incompletely into four lobes, a small dorsal and a large ventral lobe on each side (Figs. 95 and 112). The lobation does not show in a median sagittal section. The *pancreas* is represented by two outgrowths. The *ventral pancreas* originates from the hepatic diverticulum near its attachment to the duodenum (Fig. 96). It grows to the

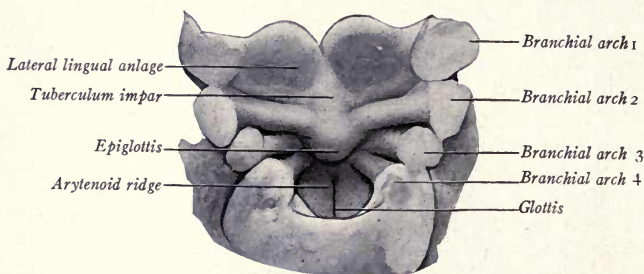


FIG. 98.—Dissection of the tongue and branchial arches of a 7 mm. pig embryo, seen in dorsal view. $\times 15$.

right of the duodenum and ventral to the portal vein. The *dorsal pancreas* takes origin from the dorsal side of the duodenum caudal to the hepatic diverticulum and grows dorsally into the substance of the gastric mesentery (Figs. 105 and 113). It is larger than the ventral pancreas, and its posterior lobules grow to the right and dorsal to the portal vein, and in later stages anastomose with the lobules of the ventral pancreas.

The *intestine* of both fore-gut and hind-gut has elongated and curves ventrally into the short umbilical cord where the yolk stalk has narrowed at its point of attachment to the gut (Fig. 96). As the intestinal tube grows ventrad, the layers of splanchnic mesoderm which attach it to the dorsal body wall grow at an equal rate and persist as the *mesentery*.

The *cloaca*, a dorso-ventrally expanded portion of the hind-gut, gives off cephalad and ventrad the *allantoic stalk*. This is at first a narrow tube, but soon expands into a vesicle of large size, a portion of which is seen in Fig. 96. Dorso-laterad the cloaca receives the *primary excretory (mesonephric) ducts*. The hind-gut is continued into the tail as the tail gut, or postanal gut, which dilates at its extremity as in the 7.8 mm. pig described

by Thyng; it soon disappears. The mid-ventral wall of the cloaca is fused to the adjacent ectoderm to form the *cloacal membrane*. In this region later the anus arises.

Urogenital System.—This consists of the *mesonephroi*, the *mesonephric (Wolffian) ducts*, the anlagen of the *metanephroi*, the *cloaca*, and the *allantois*. The form of the mesonephroi is seen in Figs. 95 and 97. Each consists of large, vascular glomeruli, associated with coiled tubules lined with cuboidal epithelium and opening into the mesonephric duct (Figs. 114 and 208). The Wolffian ducts, beginning at the anterior end of the mesonephros, curve at first along its ventral, then along its lateral surface. At its caudal end each duct bends ventrad and to the mid-plane where it opens into a lateral expansion of the cloaca (Fig. 96).

Before this junction takes place, an evagination into the mesenchyme from the dorsal wall of each mesonephric duct gives rise to the anlagen of the *metanephroi*, or permanent kidneys. A slight thickening of the mesothelium along the median and ventral surface of each mesonephros forms a light-colored area, the *genital fold* (Fig. 96). This area is pointed at either end and confined to the middle third of the kidney. It is the anlage of the *genital gland*, from which either testis or ovary is developed.

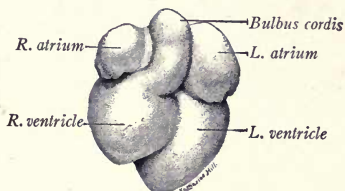


FIG. 99.—Ventral and cranial surface of the heart from a 6 mm. pig embryo. $\times 14$.

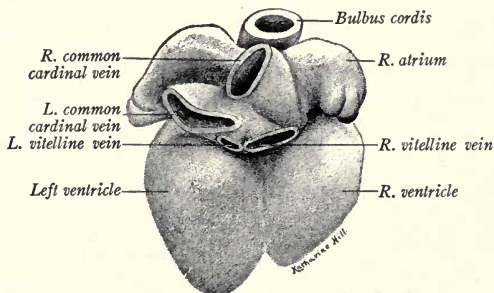


FIG. 100.—Dorsal and caudal view of the heart from a 6 mm. pig embryo. $\times 21$.

Blood Vascular System.—The *heart* lies in the pericardial cavity, as seen in Fig. 96. The atrial region (Fig. 99), as in the 4.2 mm. human embryo, has given rise to two lateral sacs, the right and left *atria*. The bulbo-ventricular loop has become differentiated into right and left *ventricles*, much thicker walled than the atria. The right ventricle is the smaller, and from it the bulbus passes between the atria and is continued as the

ventral aorta. Viewed from the caudal and dorsal aspect (Fig. 100), the *sinus venosus* is seen dorsal to the atria. It opens into the right atrium and receives from the right and left sides the paired *common cardinal veins*. These veins drain the blood from the body of the embryo. Caudally, the sinus venosus receives the two *vitelline veins*. Of these, the left is small in the liver and later disappears. The right vitelline vein, now the *common hepatic*, carries most of the blood to the heart from the umbilical veins, and from the liver sinusoids, gut, and yolk sac.

Transverse sections of the embryo through the four chambers of the heart show the atria in communication with the ventricles through the *atrio-ventricular foramina*, and the sinus venosus opening into the right atrium (Fig. 109). This opening is guarded by the right and left valves of the sinus venosus. Septa incompletely separate the two atria and the two

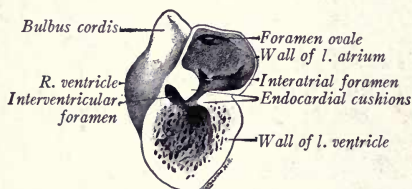


FIG. 101.—Dissection of a 5.5 mm. pig's heart from the left side, showing the septum primum and the interatrial and oval foramina. $\times 14$.

ventricles. In Fig. 109 the atrial septum (*septum primum*) appears complete due to the plane of the section. In Fig. 101, from a slightly smaller embryo, it is seen that the *septum primum* grows from the dorsal atrial wall of the heart and does not yet meet the endocardial cushions between the atrio-ventricular canals. This

opening between the atria is known as the *interatrial foramen*. Before it closes, another opening appears in the septum, dorsal in position. This is the *foramen ovale* and persists during fetal life. In Fig. 101 these two openings may be seen, as may also the dorsal and ventral *endocardial cushions* which bound the atrio-ventricular foramina. The outer mesothelial layer of the ventricles has become much thicker than that of the atria. It forms the *epicardium* and the *myocardium*, the sponge-like meshes of which are now being developed.

The Arteries.—These begin with the *ventral aorta*, which takes origin from the bulbus cordis. From the ventral aorta are given off pairs of *aortic arches*. These run dorsad in the five branchial arches (Figs. 104 and 105) and join the paired *descending aorta*. The first and second pairs of aortic arches are very small and take origin from the small common trunks formed by the bifurcation of the ventral aorta just caudal to the median thyreoid gland. The fourth aortic arch is the largest. From the apparent fifth arch small *pulmonary arteries* are developing. There is evidence that this pulmonary arch is really the sixth in the series, the fifth having been suppressed in development (cf. Fig. 272 B). Cranial to the first

pair of aortic arches, the descending aortæ are continued forward into the maxillary processes as the *internal carotids*. Caudal to the aortic arches, the descending aortæ converge, unite opposite the cardiac end of the stomach, and form the median *dorsal aorta*. From this vessel and from the descending aortæ paired, dorsal *intersegmental arteries* arise. From the seventh pair of these arteries (the first pair to arise from the median dorsal aorta) there are developed a pair of lateral branches to the upper limb buds.

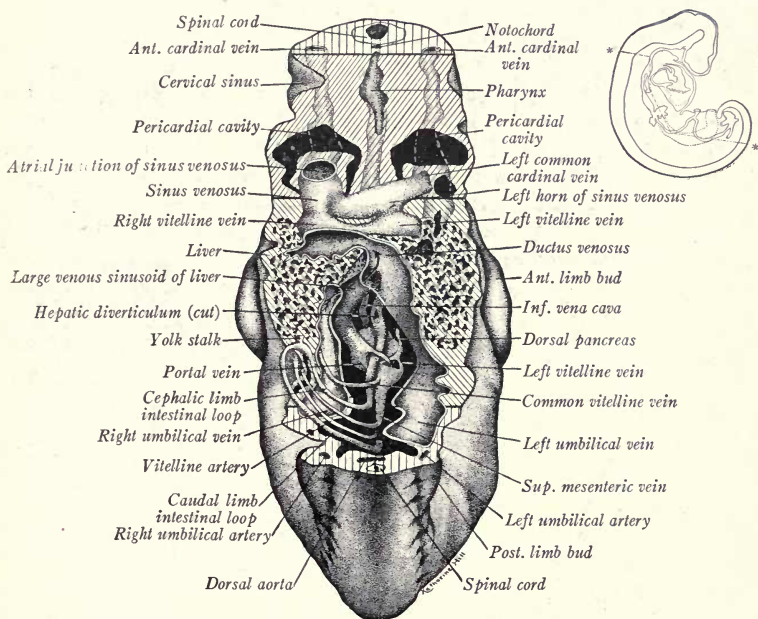


FIG. 102.—Reconstruction in ventral view of a 6 mm. pig embryo, to show the vitelline and umbilical veins, the latter opened (original drawing by K. L. Vehe). $\times 22$. In the small orientation figure (cf. Fig. 105) the various planes are indicated by broken lines—*-----*.

These vessels are the *subclavian arteries*. From the dorsal aorta there are also given off ventro-lateral arteries to the glomeruli of the mesonephros, and median ventral arteries. Of the latter, the *cæliac artery* arises opposite the origin of the hepatic diverticulum. The *vitelline artery* takes origin by two or three trunks caudal to the dorsal pancreas. Of these trunks, the posterior is the larger and persists as the superior mesenteric artery. Thyng has figured three trunks of origin in the 7.8 mm. pig. These unite and the single vitelline artery branches in the wall of the yolk sac.

Opposite the lower limb buds the dorsal aorta is divided for a short

distance. From each division there arises laterad three short trunks which unite to form the single *umbilical artery* on each side. The middle vessel is the largest and apparently becomes the common iliac artery. A pair of short caudal arteries, much smaller in size, continue the descending aortæ into the tail region.

The Veins.—The *vitelline veins*, originally paired throughout, are now represented distally by a single vessel, which, arising in the wall of the yolk sac, enters the embryo and courses cephalad of the intestinal loop (Fig. 102). Crossing to the left side of the intestine and ventral to it, it

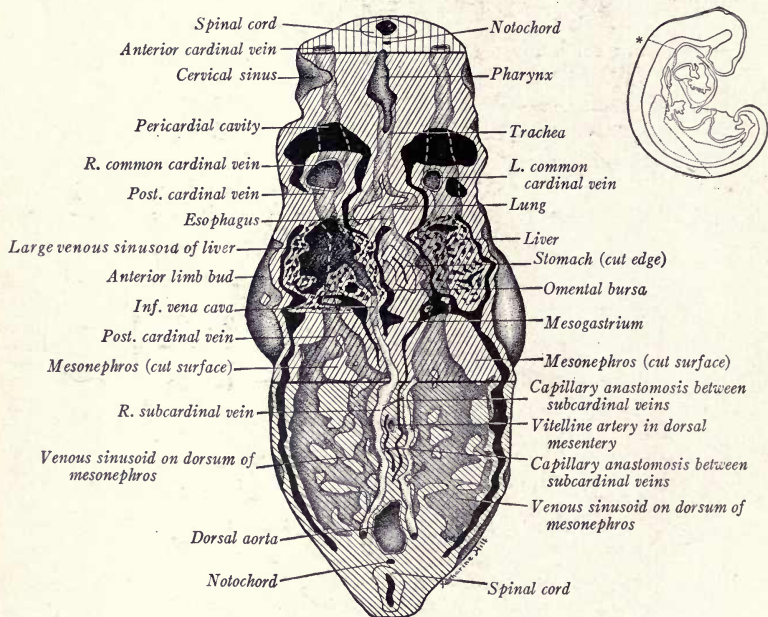


FIG. 103.—Reconstruction of the cardinal and subcardinal veins of a 6 mm. pig embryo, showing the early development of the inferior vena cava (K. L. Vehe). $\times 22$. In the small orientation figure (cf. Fig. 105) the various planes are indicated by broken lines—*.....*.

is joined by the *superior mesenteric vein* which has developed in the mesentery of the intestinal loop. The trunk formed by the union of these two vessels becomes the *portal vein*. It passes along the left side of the gut in the mesentery. Opposite the origin of the dorsal pancreas it gives off a small branch, a rudimentary continuation of the left vitelline vein, which courses cephalad and in earlier stages connects with the sinusoids of the liver. The portal vein then bends sharply to the right, dorsal to the duo-

denum, and, in the course of the right vitelline vein, passing between the dorsal and ventral pancreas to the right of the duodenum, it soon enters the liver and connects with the liver sinusoids. The portal trunk is thus formed by persisting portions of both vitelline veins, and receives a new vessel, the superior mesenteric vein. The middle portions of the primitive

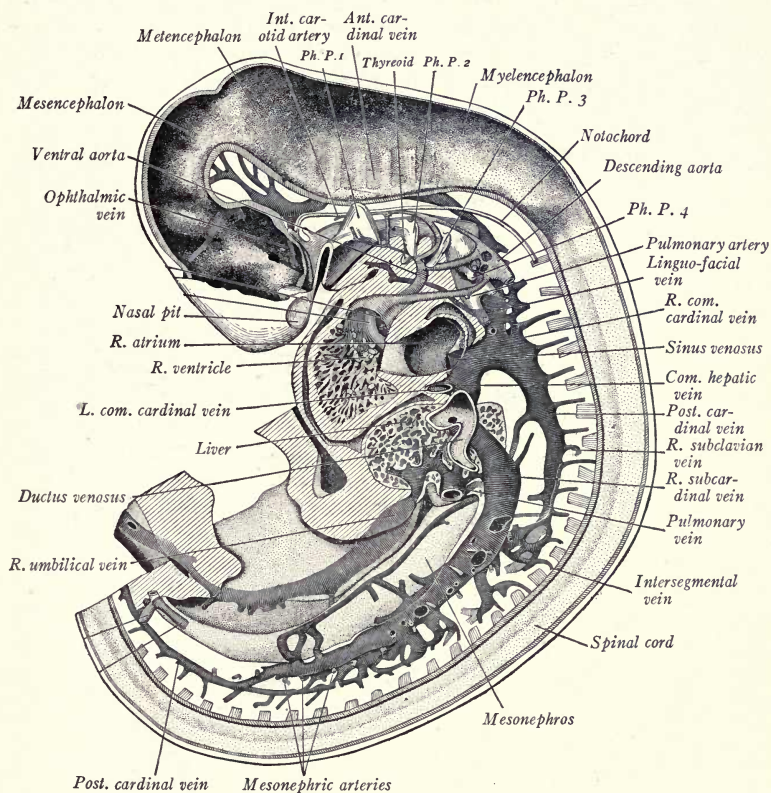


FIG. 104.—Reconstruction of 7.8 mm. pig embryo, showing veins and aortic arches from the left side (after Thyng). $\times 15$. Ph.P. 1, 2, 3, 4, Pharyngeal pouches.

vitelline veins are connected with the network of liver sinusoids. Their proximal vitelline trunks drain the blood from the liver and open into the sinus venosus of the heart. The right member of this pair is much the larger (Fig. 100) and persists as the proximal portion of the *inferior vena cava*. For the development of the portal vein see Chapter IX.

The *umbilical veins*, taking their origin in the walls of the chorion and allantoic vesicle, lie caudal and lateral to the allantoic stalk and anastomose (Figs. 102 and 105). Before the allantoic stalk enters the body, the umbilical veins separate and run lateral to the umbilical arteries. The left vein is much the larger. Both, after receiving branches from the

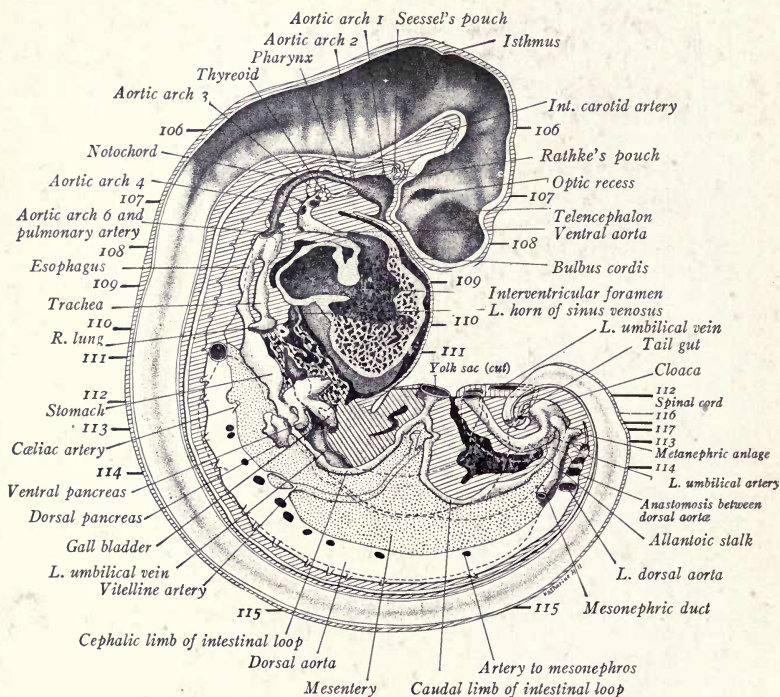


FIG. 105.—Reconstruction of a 6 mm. pig embryo in the median sagittal plane, viewed from the right side. The numbered heavy lines indicate the levels of the transverse sections shown in Figs. 106–117. The broken lines indicate the outline of the left mesonephros and the course of the left umbilical artery and vein. The latter may be traced from the umbilical cord to the liver where it is sectioned longitudinally. (Original drawing and reconstruction by K. L. Vehe). $\times 16.5$.

posterior limb buds and from the body wall, pass cephalad in the somatopleure at each side (Fig. 72). Their course is first cephalad, then dorsad, until they enter the liver. The left vein enters a wide channel, the *ductus venosus*, which carries its blood through the liver, thence to the heart by way of the right vitelline trunk. The right vein joins a large sinusoidal

continuation of the portal vein in the liver. This common trunk drains into the ductus venosus.

The *anterior cardinal veins* (Figs. 103 and 104) are formed to drain the plexus of veins on each side of the head. These vessels extend caudad and lie lateral to the ventral portion of the myelencephalon. Each anterior cardinal vein receives branches from the sides of the myelencephalon, then curves ventrad, is joined by the *linguo-facial vein* from the branchial arches and at once unites with the posterior cardinal of the same side to form the *common cardinal vein*. This, as we have seen, opens into the sinus venosus.

The *posterior cardinal veins* develop on each side in the mesonephric ridge, dorso-lateral to the mesonephros (Figs. 103, 104 and 112). Running cephalad, they join the anterior cardinal veins. When the mesonephroi become prominent, as at this stage, the middle third of each posterior cardinal is broken up into sinusoids. Sinusoids extend from the posterior cardinal vein ventrally around both the lateral and medial surfaces of the mesonephros. The median sinusoids anastomose longitudinally and form the *subcardinal veins*, right and left. The subcardinals lie along the median surfaces of the mesonephroi, more ventrad than the posterior cardinals with which they are connected at either end. There is a transverse capillary anastomosis between them, cranial and caudal to the permanent trunk of the vitelline artery (Fig. 103). The right subcardinal is connected with the liver sinusoids through a small vein which develops in the mesenchyme of the plica venæ cavæ (caval mesentery) located to the right of the mesentery (Fig. 112). This vein now carries blood direct to the heart from the right posterior cardinal and right subcardinal, by way of the liver sinusoids and the right vitelline trunk (common hepatic vein). Eventually the unpaired *inferior vena cava* forms in the course of these four vessels. (For the development of the inferior vena cava see Chapter IX.)

TRANSVERSE SECTIONS OF A SIX MM. PIG EMBRYO

Having acquainted himself with the anatomy of the embryo from the study of dissections and reconstructions, the student should examine serial sections cut in the plane indicated by guide lines on Fig. 105. Refer back to the external structure of the embryo (Fig. 93), to the lateral dissection of the organs (Fig. 95), and having determined the exact plane of each section, interpret the structures seen by comparing with Fig. 105. The various structures may be recognized by referring to the figures of sections in the text, and they should be traced section by section through the series as carefully as time will allow. Remember that the sections of pig embryos figured here are drawn from the cephalic surface, so that the right side of the section is the left side of the embryo.

Section through the Myelencephalon and Otocysts of a 6 mm. Embryo (Fig. 106).—As the head is bent nearly at right angles to the body, this section passes lengthwise through the myelencephalon. The *diencephalon* is cut transversely. The cellular walls of the myelencephalon show a series of six pairs of constrictions, the *neuromeres*. Lateral to the fourth pair of neuromeres are the *otocysts*, which show a median outpocketing at the point of entrance of the *endolymph duct*. The *ganglia* of the nn. trigeminus, facialis, acusticus, and the superior ganglion of the glossopharyngeal nerve occur in order on each side. Sections of the anterior cardinal vein and its branches show on the left side. Ventral to the diencephalon are sections of the *internal carotid arteries*.

Passing along down the series into the pharynx region, observe the first, second, and third *pharyngeal pouches*. Their dorsal diverticula come into contact with the ectoderm of the branchial clefts and form the *closing plates*.

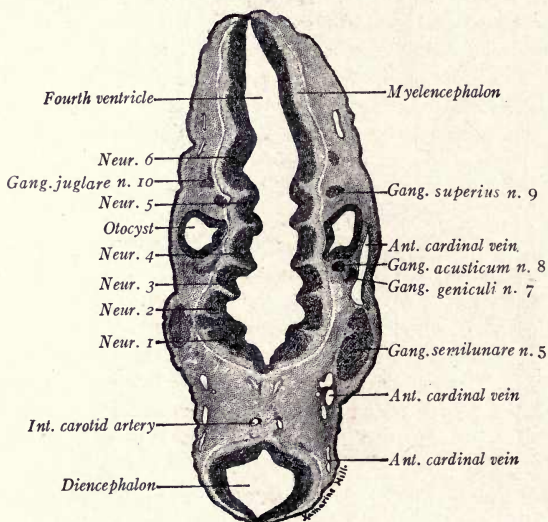


FIG. 106.—Transverse section through the myelencephalon and otocysts of a 6 mm. pig embryo. $\times 26.5$. Neur. 1-6, neuromeres 1-6.

Section through the Branchial Arches and the Eyes (Fig. 107).—The section passes lengthwise through the four branchial arches, the fourth sunken in the cervical sinus. Dorsad is the spinal cord with the first pair of cervical ganglia. The *pharynx* is cut across between the third and fourth branchial pouches. In its floor is a prominence, the anlage of the *epiglottis*. Ventral to the pharynx the ventral aorta gives off two pairs of vessels. The larger pair are the *fourth aortic arches* which curve dorsad around the pharynx to enter the *descending aortæ*. The smaller *third aortic arches* enter the third branchial arches on each side. A few sections higher up in the series the ventral aorta bifurcates, and the right and left trunks thus formed give off the *first and second pair of aortic arches*. Cranially, in the angle between their common trunks, lies the median *thyreoid anlage*. The *anterior cardinal veins* are located lateral and dorsal to the descending aortæ. The end of

the head is cut through the *diencephalon* and the *optic vesicles*. On the left side of the figure the *lens vesicle* may be seen still connected with the ectoderm. The optic vesicle now shows a thick inner, and a thin outer layer; these form the *nervous* and *pigment layers* of the retina respectively.

Section through the Tracheal Groove, Bulbus Cordis and Olfactory Pits (Fig. 108).—The ventral portion of the figure shows a section through the tip of the head. The *telencephalon* is not prominent. The ectoderm is thickened and slightly invaginated ventro-laterad to form the anlagen of the *olfactory pits*. These deepen in later stages and become the nasal cavities. In the dorsal portion of the section may be seen the cervical portion of the *spinal cord*, the *notochord* just ventral to it, the *descending aortæ*, and ventro-lateral

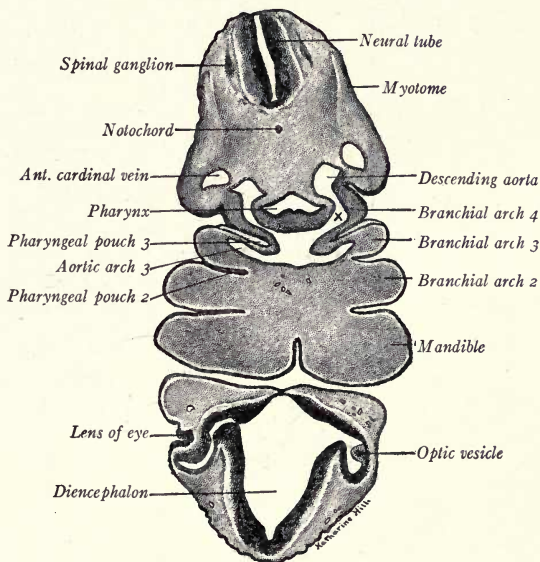


FIG. 107.—Transverse section through the branchial arches and eyes of a 6 mm. pig embryo. $\times 26.5$. X, aortic arch 4.

to them the *anterior cardinal veins*. The nasopharynx now is small with a vertical groove in its floor. This is the tracheal groove and more caudad it will become the cavity of the *trachea*. The *bulbus cordis* lies in the large *pericardial cavity*. On either side the section cuts through the cephalic portions of the *atria*. These will become larger as we go caudad in the series.

Section through the Heart (Fig. 109).—Lateral to the descending aortæ are the *common cardinal veins*. The right common cardinal opens into the *sinus venosus* which in turn empties into the right atrium, its opening being guarded by the two *valves of the sinus venosus*. The entrance of the left common cardinal into the sinus venosus is somewhat more caudad in the series. The *trachea* has now separated from the *esophagus* and lies ventral to it. Both trachea and esophagus are surrounded by a condensation of mesen-

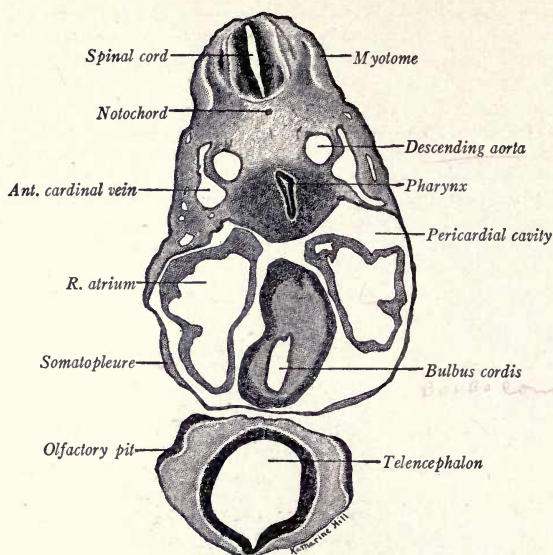


FIG. 108.—Transverse section through the bulbus cordis and olfactory pits of a 6 mm. pig embryo. $\times 26.5$.

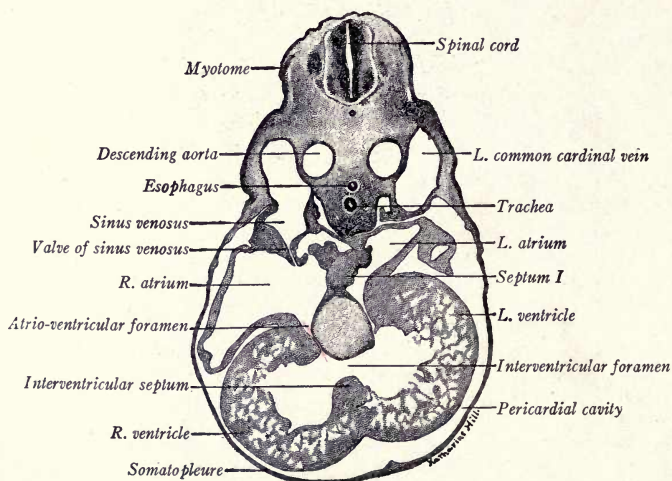


FIG. 109.—Transverse section through the four chambers of the heart of a 6 mm. pig embryo. $\times 26.5$.

chyme. The myocardium of the ventricles has formed a spongy layer, much thicker than that of the atrial wall. An incomplete *interventricular septum* leaves the ventricles in communication dorsad. The *septum primum* is complete in this section, but higher up in the series there is an *interatrial foramen* (cf. Fig. 101). The *foramen ovale* is hardly formed.

Section through the Lung Buds and Septum Transversum (Fig. 110).—The section passes through the bases of the *upper limb buds*. The tips of the ventricles, lying in the pericardial cavity, still show in this section. Dorsally, the pericardial cavity has given place to the *pleuro-peritoneal* cavity. Projecting ventrad into this cavity are the *mesonephric* (Wolffian) folds in which the *posterior cardinal veins* partly lie. Into the floor of the pleuro-peritoneal cavities bulge the dorsal lobes of the *liver*, embedded in mesenchyma. This mesenchyma is continuous with that of the somatopleure, and forms a complete transverse septum ventrally between the liver and heart. This is the *septum transversum* which

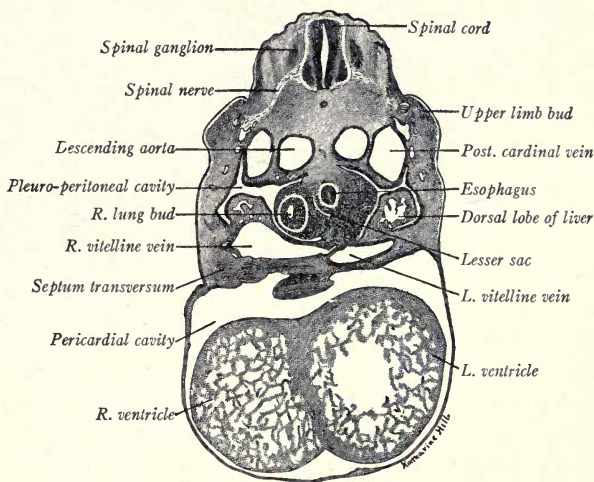


FIG. 110.—Transverse section through the right lung bud and septum transversum of a 6 mm. pig embryo. $\times 26.5$.

takes part in forming the ligaments of the liver and is the anlage of a portion of the *diaphragm*. The two proximal trunks of the *vitelline veins* pass through the septum. Projecting laterally into the pleuro-peritoneal cavities are ridges of mesenchyma covered by splanchnic mesoderm in which the lungs develop as lateral buds from the caudal end of the trachea. The right *lung bud* is shown in the figure. Between the esophagus and the lung is a crescent-shaped cavity, the cranial end of the *lesser peritoneal sac*.

Section through the Stomach (Fig. 111).—The section passes through the upper *limb buds* and just caudal to the point at which the descending aortae unite to form the median dorsal aorta. As the liver develops in early stages, it comes into relation with the *plica venae cavae* along the dorsal body wall at the right side of the dorsal mesogastrium. The space between the liver and plica to the right, and the stomach and its omenta to the left, is a caudal continuation of the *lesser peritoneal sac*. The dorsal wall of the *stomach*

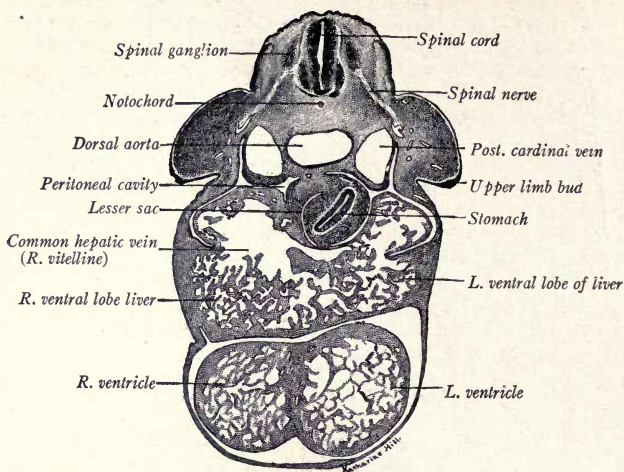


FIG. 111.—Transverse section through the stomach of a 6 mm. pig embryo. $\times 26.5$.

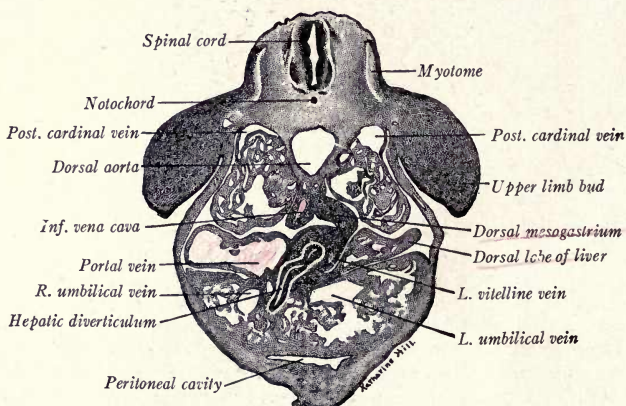


FIG. 112.—Transverse section through the hepatic diverticulum of a 6 mm. pig embryo. $\times 26.5$.

is rotated to the left, its ventral wall to the right. The *liver* shows a pair of dorsal lobes and contains large blood spaces and networks of *sinusoids* lined with endothelium. Ventral to the liver, the tips of the ventricles are seen.

Section through the Hepatic Diverticulum (Fig. 112).—The upper limb buds are prominent in this section. The mesonephric folds show the tubules and glomeruli of the *mesonephroi*, and the *posterior cardinal veins* are connected with the mesonephric sinusoids. From the dorsal attachment of the liver there is continued down into this section a ridge on the dorsal body wall just to the right (left in figure) of the mesentery. In this ridge lies a small vein which connects cranially with the liver sinusoids, caudally with the right subcardinal vein. As it later forms a portion of the *inferior vena cava*, the ridge in which it lies is termed the *plica venæ cavæ*, or *caval mesentery*. The right dorsal lobe of the liver contains a large blood space into which the *portal vein* opens. The duodenum is ventral to the position occupied by the stomach in the previous section. There is given off from it ventrad and to the right the *hepatic diverticulum*. In the sections higher up, small ducts from the liver trabeculae may be traced into connection with it. In the left ventral lobe of the liver, a large blood space indicates the position of the *left umbilical vein* on its way to the ductus venosus.

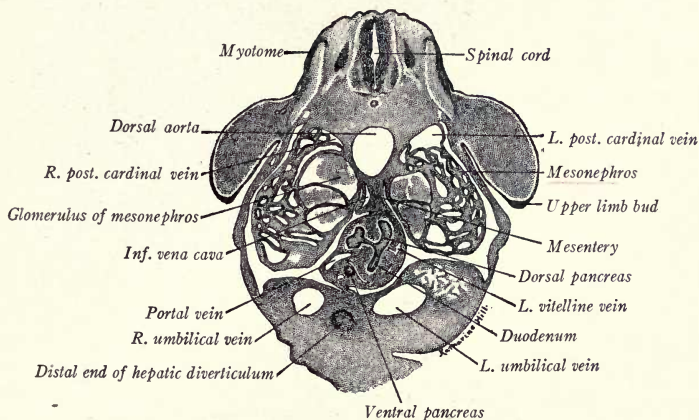


FIG. 113.—Transverse section through the dorsal pancreas of a 6 mm. pig embryo. $\times 26.5$.

Section through the Dorsal Pancreas (Fig. 113).—At this level the upper limb buds still show; the mesonephroi are larger and marked by their large glomeruli. The *right posterior cardinal vein* is broken up into mesonephric sinusoids. The vein in the *plica venæ cavæ* will, a few sections lower, connect with the right subcardinal vein. The anlage of the *dorsal pancreas* is seen extending from the duodenum dorsad into the mesenchyme of the mesentery. It soon bifurcates into a dorsal and right lobe, of which the latter is slightly lobulated. Ventro-lateral to the duodenum the anlage of the *ventral pancreas* is seen cut across. It may be traced cephalad in the series to its origin from the hepatic diverticulum. To the right of the ventral pancreas lies the *portal vein* (at this level a portion of the right vitelline). To the left of the dorsal pancreas is seen the remains of the *left vitelline vein*. The ventral lobes of the liver are just disappearing at this level. In the mesenchyme that connects the liver with the ventral body wall lie on each side the *umbili-*

cal veins, the left being the larger. Between the veins is the extremity of the *hepatic diverticulum*. The body wall is continued ventrad to form a short *umbilical cord*.

Section at the Level of Origin of the Vitelline and Umbilical Arteries (Fig. 114).—As the posterior half of the embryo is curved in the form of a half circle, sections caudal to the liver, like this one, pass through the lower end of the body at the level of the *posterior limb buds*. Two sections of the embryo are thus seen in one, their ventral aspects

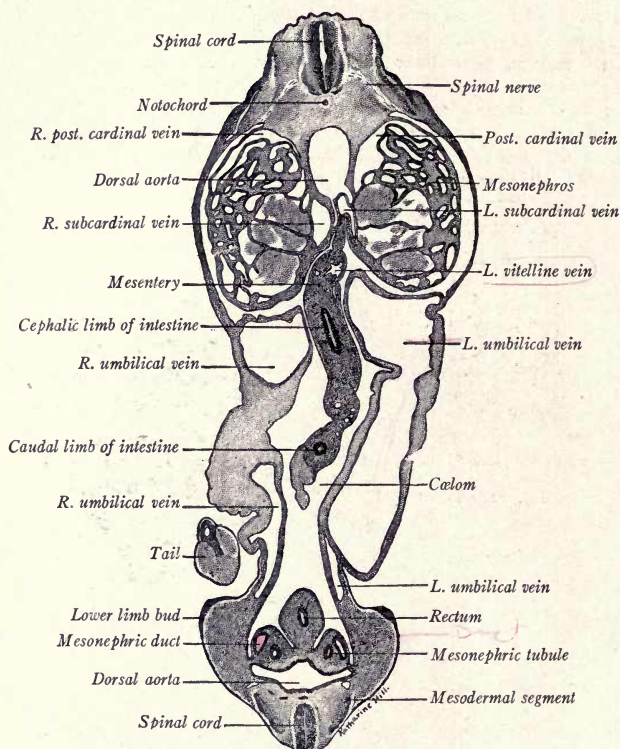


FIG. 114.—Transverse section of a 6 mm. pig embryo at the level of the origin of the vitelline artery. The lower end of the section passes through the posterior limb buds. $\times 26.5$.

facing each other and connected by the lateral body wall. In the dorsal part of the section the *mesonephroi* are prominent, with large *posterior cardinal veins* lying dorsal to them. The trunk of the *vitelline artery* takes origin ventrally from the aorta. It may be traced into the mesentery, and through it into the wall of the yolk sac. On either side of the vitelline artery are the *subcardinal veins*, the right being the larger. In the mesentery may be seen two sections of the intestinal loop (the *small intestine* being cut lengthwise, the *large intestine* transversely), and also sections of the *vitelline artery* and *veins*. In the lateral

body walls, ventral to the mesonephros, occur the *umbilical veins*. The left vein is large and cut lengthwise. The right vein is cut obliquely twice.

In the ventral portion of the section, the *lower limb buds* are prominent laterally. A large pair of arteries, the *common iliacs*, are given off from the aorta and may be traced into connection with the *umbilical arteries*. The *large intestine*, supported by a short *mesentery*, lies in the coelom near the midplane. On each side are the *mesonephric folds*, here small and each showing a section of the *mesonephric duct* and a single vesicular anlage of the *mesonephric tubules*. The mesonephric ducts are sectioned as they curve around from their position in the dorsal portion of the section.

Section through the Primitive Segments and Spinal Cord (Fig. 115).—This section is near the end of the series, and, as the body is here curved, it is really a frontal section. At the left side of the spinal cord, the oval cellular masses are the *spinal ganglia* cut across.

The ectoderm, arching over the segments, indicates their position. Each segment shows an outer dense layer, the *dermatome*, lying just beneath the ectoderm. This plate curves lateral to the spindle-shaped *myotome*, which gives rise to the voluntary muscle. Next comes a diffuse mass of mesenchyma, the *sclerotome*, which eventually, with its

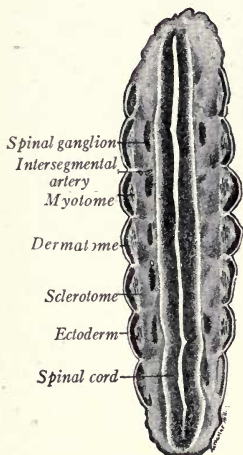


FIG. 115.—Transverse section through the primitive segments and spinal cord of a 6 mm. pig embryo. $\times 45$.

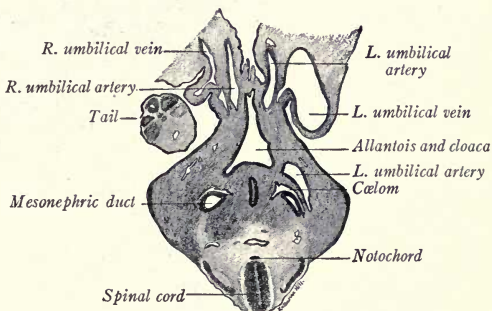


FIG. 116.—Transverse section through the umbilical vessels, allantois and cloaca of a 6 mm. pig embryo. $\times 45$.

fellow of the opposite side, surrounds the spinal cord and forms the anlage of a vertebra. A pair of spinal nerves and spinal ganglia are developed opposite each somite, and pairs of small vessels are seen between the segments. These are dorsal *intersegmental arteries*.

Section through the Umbilical Vessels, Allantois and Cloaca (Fig. 116).—Having now studied sections at various levels to near the end of the series, we shall next examine sections through the caudal region and study the anlagen of the urogenital organs. Owing to the curvature of the embryo, it is necessary to go cephalad in our series. The first section passes through the bases of the limb buds at the level where the *allantoic stalk*, curving inward from the umbilical cord, opens into the *cloaca*. At either side of the allantoic stalk may be seen oblique sections of the *umbilical arteries*, and lateral to these the large left and small right *umbilical vein*. The *mesonephric ducts* occupy the mesonephric ridges which project into small caudal prolongations of the coelom. Midway between the

ducts lies the *hind-gut*, dorsal to the cloaca. The tip of the tail is seen in section at the left of the figure.

Section through the Anlages of the Metanephroi, Cloaca and Hind-gut (Fig. 117).—The *metanephroi* are seen as dorsal evaginations from the mesonephric (Wolffian) ducts just before their entrance into the cloaca. Each consists of an epithelial layer surrounded by a condensation of mesenchyme. Traced a few sections cephalad the *mesonephric ducts* open into the lateral diverticula of the *cloaca*, which, irregular in outline because it is sectioned obliquely, lies ventral to them and receives dorsad the *hind-gut*. Caudal to the cloaca in this embryo the tail bends abruptly cephalad and to the right. The blind prolongation of the hind-gut may be traced out into this portion of the tail until it ends in a sac-like dilatation.

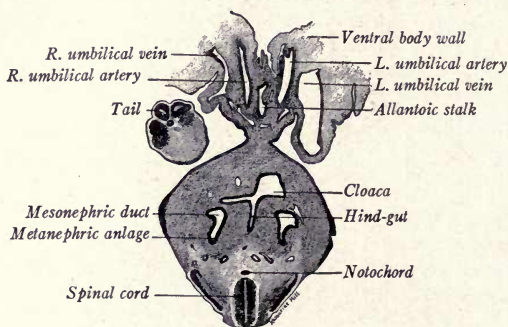


FIG. 117.—Transverse section through the anlagen of the metanephroi of a 6 mm. pig embryo. $\times 45$.

B. THE ANATOMY OF TEN TO TWELVE MM. PIG EMBRYOS

The study of embryos at this stage is important as they possess the anlagen of most of the organs. The anatomy of a 12 mm. pig embryo has been carefully studied and described by Lewis (*Amer. Jour. Anat.*, vol. 2, 1903).

External Form (Fig. 118).—The head is now relatively large on account of the increased size of the brain. The third branchial arch is still visible in the embryo, but the fourth arch has sunken in the *cervical sinus*; usually both have disappeared at a slightly later stage. The *olfactory pits* form elongated grooves on the under surface of the head, and the *lens* of the eye lies beneath the ectoderm, surrounded by the *optic cup*. The *maxillary* and *mandibular* processes of the first branchial arch are larger, and the former shows signs of fusing with the median nasal process to form the upper jaw. Small tubercles, the anlagen of the *external ear*, have developed about the first branchial cleft which itself becomes the *external auditory meatus*.

At the cervical bend the head is flexed at right angles with the body, bringing the ventral surface of the head close to that of the trunk, and

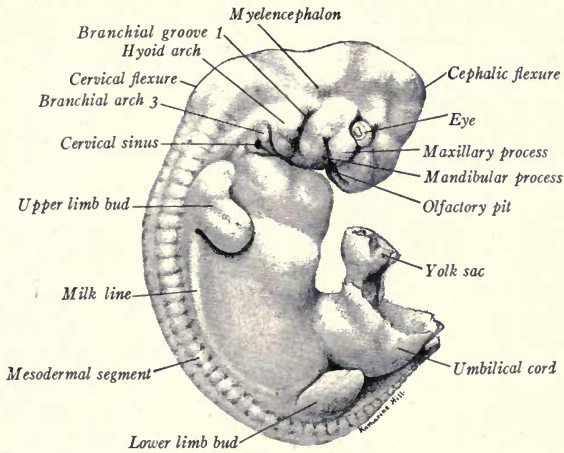


FIG. 118.—Exterior of a 10 mm. pig embryo, viewed from the right side. $\times 7$.

it is probably owing to this flexure that the third and fourth branchial arches buckle inward to form the cervical sinus. Dorsad, the trunk forms

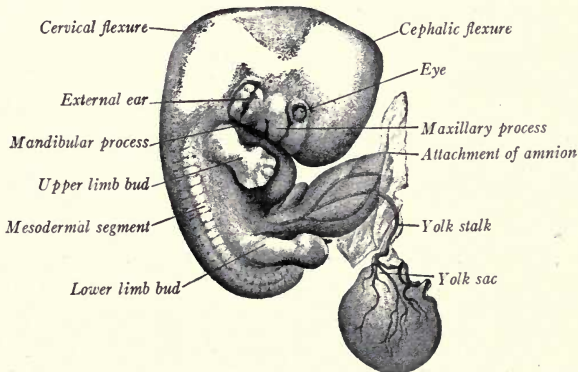


FIG. 119.—Exterior of a human embryo of 12 mm. viewed from the right side, showing attachment of amnion (cut away) and yolk stalk and sac. $\times 4$.

a long curve more marked opposite the posterior extremities. The reduction in the trunk flexures is due to the increased size of the heart, liver, and mesonephroi. These organs may be seen through the translu-

cent body wall, and the position of the *septum transversum* may be noted between the heart and the liver, as in Fig. 120. The limb buds are larger and the umbilical cord is prominent ventrad. Dorsally, the mesodermal segments may be seen, and, extending in a curve between the bases of the limb buds, is the *milk line*, a thickened ridge of ectoderm which forms the

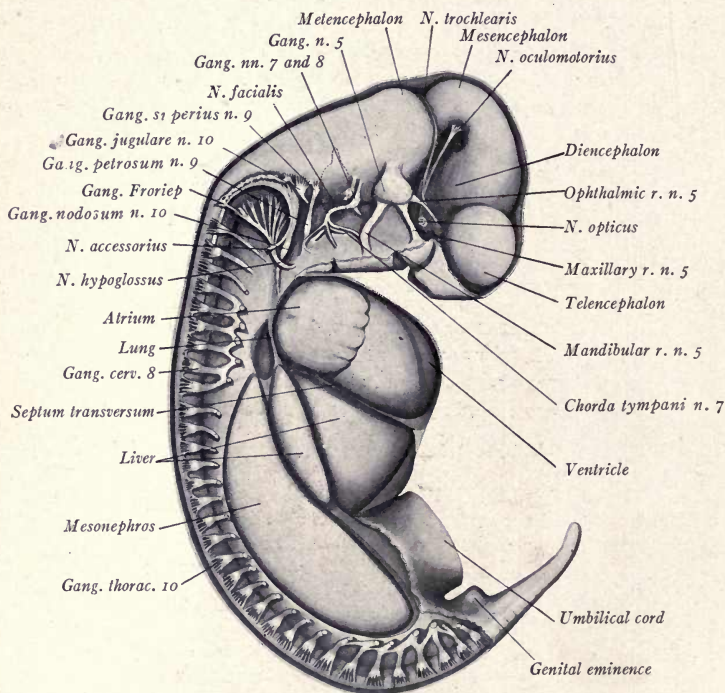


FIG. 120.—Lateral dissection of a 10 mm. pig embryo, showing the viscera and nervous system from the right side. The eye has been removed and the otic vesicle is represented by a broken line. The ventral roots of the spinal nerves are not indicated. $\times 10.5$. n., Nerve; r., ramus.

anlages of the *mammary glands*. The tail is long and tapering. Between its base and the umbilical cord is the *genital eminence* (Fig. 120).

Human embryos of this stage or slightly older vary considerably in size (Fig. 119). They differ from pig embryos in the greater size of the head, the shorter tail, the much smaller mesonephric region, the longer umbilical cord, and the less prominent segments. The *yolk sac* is pear-shaped and the *yolk stalk* is long and slender.

Central Nervous System.—Dissections show well the form and relations of the organs (Figs. 120, 121 and 122). Directions for preparing dissections are given in Chapter VI.

The Brain.—Five distinct regions may be distinguished (Figs. 120 and 122): (1) The *telencephalon* with its rounded lateral outgrowths, the *cerebral hemispheres*. Their cavities, the *lateral ventricles*, communicate by the *interventricular foramina* with the third ventricle. (2) The *diencephalon* shows a laterally flattened cavity, the *third ventricle*. Ventro-laterally from the diencephalon pass off the optic stalks, and an evagination of the mid-ventral wall is the anlage of the *posterior hypophyseal*

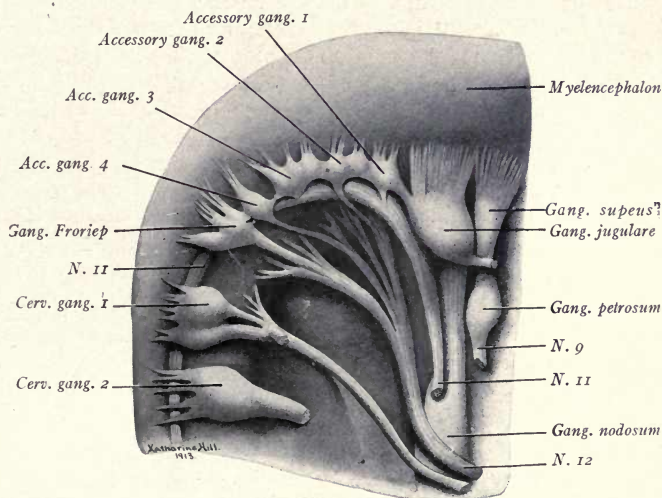


FIG. 121.—Dissection of the head of a 15 mm. pig embryo from the right side, to show the accessory vagus ganglia with peripheral roots passing to the hypoglossal nerve. $\times 25$.

lobe. (3) The *mesencephalon* is undivided, but its cavity becomes the *cerebral aqueduct* leading caudally into the fourth ventricle. (4) The *metencephalon* is separated from the mesencephalon by a constriction, the *isthmus*. Dorso-laterally it becomes the *cerebellum*, ventrally the *pons*. (5) The elongated *myelencephalon* is roofed over by a thin, non-nervous ependymal layer. Its ventro-lateral wall is thickened and still gives internal indication of the *neuromeres*. The cavity of the metencephalon and myelencephalon is the *fourth ventricle*.

The Cerebral Nerves.—Of the twelve cerebral nerves, all but the first (olfactory) and sixth (abducens) are represented in Fig. 120. For a detailed description of these nerves see Chapter XIII. (2) The *optic*

nerve is represented by the optic stalk cut through in Fig. 120. (3) The *oculomotor*, a motor nerve to four of the eye muscles, takes origin from the ventro-lateral wall of the mesencephalon. (4) The *trochlear nerve* fibers, motor, to the superior oblique muscle of the eye, arise from the ventral wall of the mesencephalon, turn dorsad and cross at the isthmus, thus emerging on the opposite side. From the myelencephalon arise in order: (5) the *n. trigeminus*, mixed, with its *semilunar ganglion* and three branches, the *ophthalmic*, *maxillary*, and *mandibular*; (6) the *n. abducens*, motor, from the ventral wall to the external rectus muscle of the eye; (7) the *n. facialis*, mixed, with its *geniculate ganglion* and its *chorda tympani*, *facial*, and *superficial petrosal branches* in the order named; (8) the *n. acusticus*, sensory, arising cranial to the otocyst, with its *acoustic ganglion* and sensory fibers to the internal ear; (9) caudal to the otocyst the *n. glossopharyngeus*, mixed, with its *superior* and *petrosal ganglia*; (10) the *n. vagus*, sensory, with its *jugular* and *nodose ganglia*; (11) the *n. accessorius*, whose motor fibers take origin from the lateral wall of the spinal cord and myelencephalon between the jugular and sixth cervical ganglia; the internal branch of the *n. accessorius* accompanies the vagus; the external branch leaves it between the jugular and nodose ganglia and supplies the sternocleidomastoid and trapezius muscles; (12) the *n. hypoglossus*, motor, arising by five or six fascicles from the ventral wall of the myelencephalon; its trunk passes lateral to the nodose ganglion and supplies the muscles of the tongue.

A nodular chain of ganglion cells extends caudad from the jugular ganglion of the vagus. These have been interpreted as *accessory vagus ganglia*. They may, however, be continuous with *Froriep's ganglion* which sends sensory fibers to the *n. hypoglossus*. In pig embryos of 15 to 16 mm. this chain is frequently divided into four or five ganglionic masses, of which occasionally two or three (including Froriep's ganglion) may send fibers to the root fascicles of the hypoglossal nerve. Such a condition is shown in Fig. 121.

The Spinal Nerves.—Each of these has its own *spinal ganglion*, from which the dorsal root fibers are developed (Figs. 120 and 136). The motor fibers take origin from the ventral cells of the neural tube and form the ventral roots which join the dorsal roots in the nerve trunk.

Besides the nervous system, Fig. 120 also shows the *heart*, with its right *atrium* and *ventricle*, the dorsal and ventral lobes of the *liver*, and the prominent *mesonephros*. Dorsal and somewhat caudal to the atrium is the anlage of the *right lung*. The *septum transversum* extends between the heart and the liver.

Pharynx and its Derivatives.—Dorsally, the anterior lobe of the hypophysis is long and forks at its end (Figs. 122 and 123). In the floor

of the pharynx are the anlagen of the *tongue* and *epiglottis* (Fig. 156 A). From each mandibular arch arises an elongated thickening that extends caudal to the second arch. Between, and fused to these thickenings, is the triangular *tuberculum impar*. The opening of the *thyreoglossal duct* between the tuberculum impar and the second arch is early obliterated. A median ridge, or *copula*, between the second arches connects the tuber-

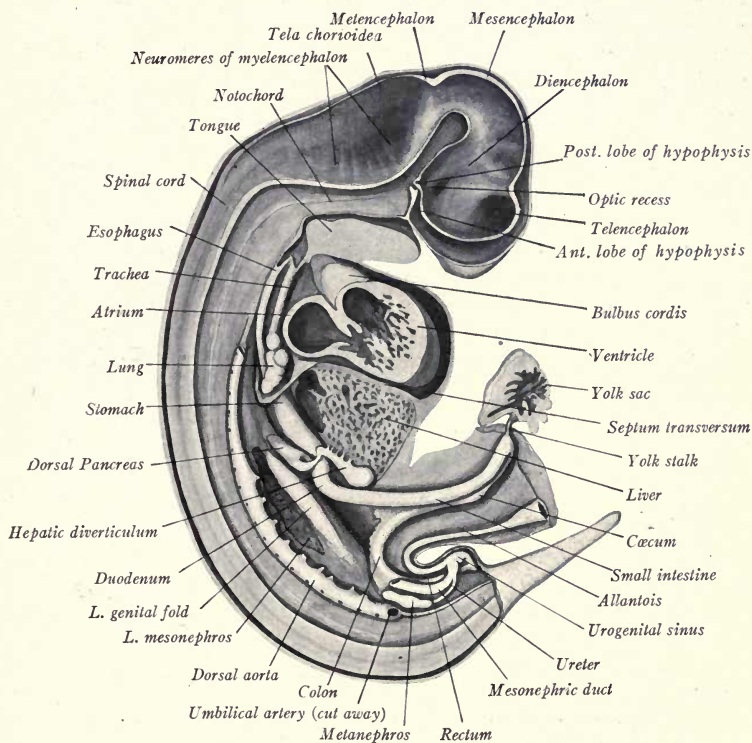


FIG. 122.—Median sagittal dissection of a 10 mm. pig embryo, showing the brain, spinal cord and viscera from the right side. $\times 10.5$.

culum impar with the epiglottis, which seems to develop from the bases of the third and fourth branchial arches. On either side of the slit-like glottis are the *arytenoid folds* of the larynx. (For the development of the tongue, see p. 149.) The *pharyngeal pouches* are now larger than in the 6 mm. pig (Fig. 123). The first pouch persists as the *auditory tube* and *middle ear cavity*, the 'closing plate' between it and the first branchial cleft

forming the *tympanic membrane*. The second pouch later largely disappears; about it, develops the *palatine tonsil*. The third pouch is tubular, directed at right angles to the pharynx, and meets the ectoderm to form a closing plate. Median to the plate, the ventral diverticulum of the third pouch is the anlage of the *thymus gland*. Its dorsal diverticulum forms an epithelial body, or *parathyreoid*. The fourth pouch is smaller and its

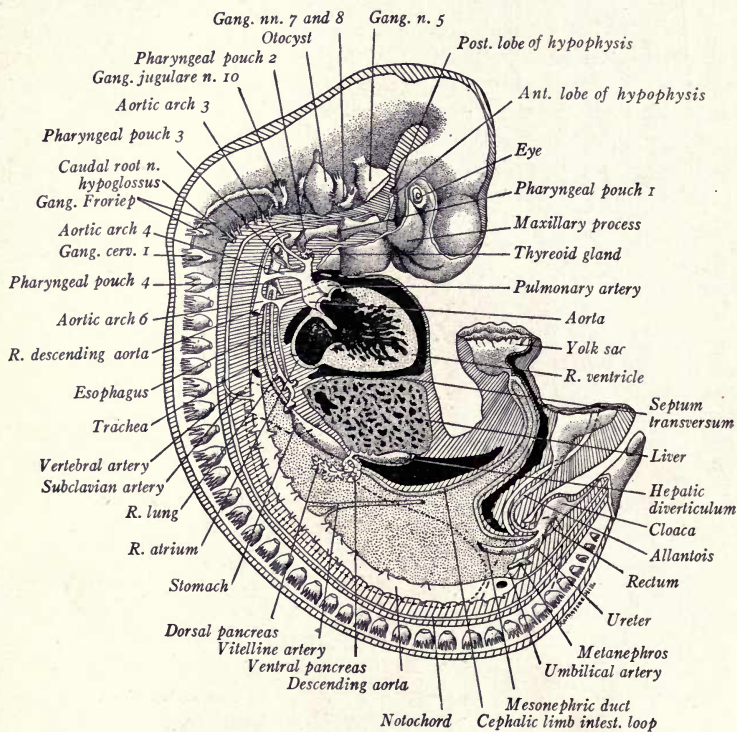


FIG. 123.—Reconstruction of a 10 mm. pig, to show the position of the various organs from the right side. The veins are not indicated. Broken lines indicate the outline of the left mesonephros and the positions of the limb buds. $\times 10$.

dorsal diverticulum gives rise to a second parathyreoid body. Its ventral diverticulum is a rudimentary thymus anlage. A tubular outgrowth, caudal to the fourth pouch, is regarded as a fifth pharyngeal pouch in human embryos and forms the *ultimobranchial body* on each side (see p. 165). The *thyroid gland*, composed of branched cellular cords, is located in the midplane between the second and third branchial arches (Fig. 123).

Trachea and Lungs.—Caudal to the fourth pharyngeal pouches, the esophagus and trachea separate and form entodermal tubes (Figs. 122 and 123). Cephalad of the point where the trachea bifurcates to form the *primary bronchi* there appears on its right side the tracheal bud of the upper lobe of the right lung (Fig. 124). This bronchial bud is developed only on the right side and appears in embryos of 8 to 9 mm. Two secondary bronchial buds arise from the primary bronchus of each lung, and form the anlagen of the symmetrical lobes of each lung.

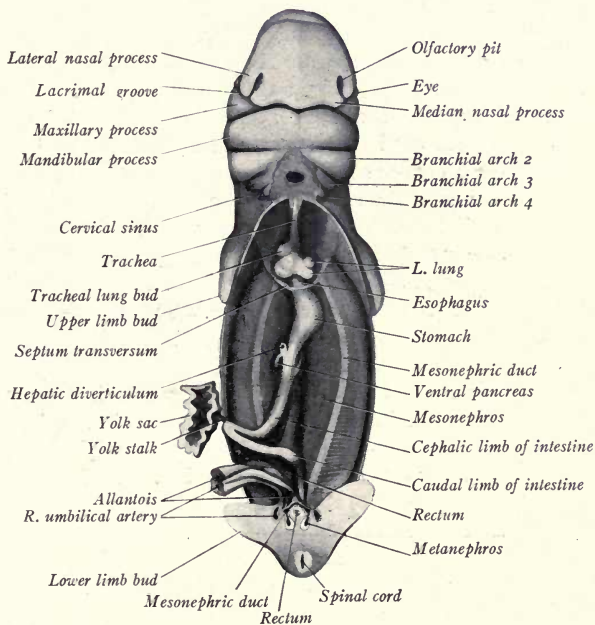


FIG. 124.—Ventral dissection of a 9 mm. pig embryo. The head is bent dorsad. $\times 9$.

Esophagus and Stomach.—The *esophagus* extends as a narrow tube caudal to the lungs, where it dilates into the stomach. The *stomach* is wide from its greater to its lesser curvature and shows a *cardiac diverticulum* (Lewis). The pyloric end of the stomach has rotated more to the right, where it opens into the *duodenum*, from which division of the intestine the liver and pancreas develop.

The *liver*, with its four lobes, fills in the space between the heart, stomach, and duodenum (Fig. 122). Extending from the right side of the duodenum along the dorsal and caudal surface of the liver is the hepatic

diverticulum. It lies to the right of the midplane and its extremity is saccular. This saccular portion becomes the *gall bladder*. Several ducts connect the diverticulum with the liver cords. One of these persists as the *hepatic duct* which joins the *cystic duct* of the gall bladder. The portion of the diverticulum proximal to this union becomes the common bile duct, or *ductus choledochus*. The *ventral pancreas* arises from the common bile duct near its point of origin (Fig. 123). It is directed dorsad and caudad to the right of the duodenum. The *dorsal pancreas* arises more caudally from the dorsal wall of the duodenum and its larger, lobulated body grows dorsally and cranially (Figs. 123, 127 and 140). Between the pancreatic anlagen courses the portal vein. In the pig, the duct of the dorsal pancreas persists as the functional duct.

Intestine.—Caudal to the duodenum, the intestinal loop extends well into the umbilical cord (Figs. 122 and 123). At the bend of the intestinal loop is the slender *yolk stalk*. The cephalic limb of the intestine lies to the right, owing to the rotation of the loop. The small intestine extends as far as a slight enlargement of the caudal limb of the loop, the anlage of the *cæcum*, or blind gut. This anlage marks the beginning of the *large intestine* (colon and rectum). The intestinal loop is supported by the *mesentery* which is cut away in Fig. 122. The cloaca is now nearly separated into the *rectum* and *urogenital sinus*. The cavity of the rectum is almost occluded by epithelial cells (Lewis).

Urogenital System.—The *mesonephros* is much larger and more highly differentiated than in the 6 mm. embryo (Figs. 120 and 124). Along the middle of its ventro-median surface the *genital fold* is now more prominent (Fig. 122). In a ventral dissection (Fig. 124) the course of the *mesonephric ducts* may be traced. They open into the *urogenital sinus*, which also receives the *allantoic stalk* (Fig. 122).

The *metanephros*, or permanent kidney anlage, lies just mesial to the umbilical arteries where they leave the aorta (Fig. 123). Its epithelial portion, derived from the mesonephric duct, is differentiated into a proximal, slender duct, the *ureter*, and into a distal, dilated *pelvis*. From this grow out later the *calyces* and *collecting tubules* of the kidney. Surrounding the pelvis is a layer of condensed mesenchyma, or *nephrogenic tissue*, which is the anlage of the remainder of the kidney.

Blood Vascular System.—*The Heart.*—In Fig. 125 the cardiac chambers of the right side are opened. The *septum primum* between the atria is perforated dorsad and cephalad by the *foramen ovale*. The *inferior vena cava* is seen opening into the *sinus venosus*, which in turn communicates with the right atrium through a sagittal slit guarded by the right and left *valves of the sinus venosus*. The right valve is the higher and its dorsal half is cut away. The valves were united cephalad as the *septum spurium*.

Between the left valve and the septum primum, the sickle-like fold of the *septum secundum* is forming; the fusion of these three components gives rise later to the adult atrial septum. The aortic bulb is divided distally into the *aorta* and the *pulmonary artery*, the latter connecting with the sixth (apparent fifth) pair of aortic arches. Proximally the bulb is undivided. The *interventricular septum* is complete except for the *interventricular foramen* which leads from the left ventricle into the aortic side of the bulb. Of the *bulbar swellings* which divide the bulb into aorta and pulmonary trunk, the *left* joins the interventricular septum, while the *right* extends to the endocardial cushion. These folds eventually fuse and the partition of the ventricular portion of the heart is completed.

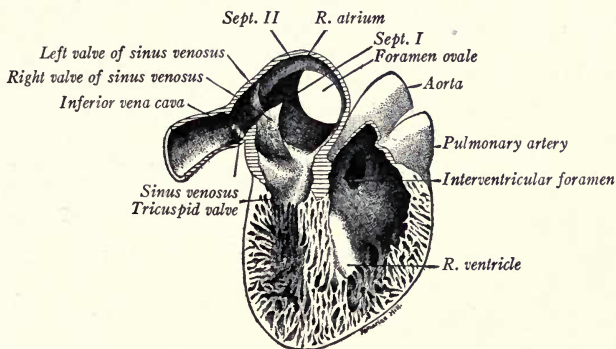


FIG. 125.—Heart of 12 mm. embryo, dissected from the right side.

The endocardium at the atrio-ventricular foramina is already undermined to form the anlagen of the *tricuspid* and *bicuspid* valves. From the caudal wall of the left atrium there is given off a single *pulmonary vein*.

The Arteries.—As seen in Fig. 123, the first two aortic arches have disappeared. Cranial to the third arch, the ventral aortæ become the *external carotids*. The third aortic arches and the cephalic portions of the descending aortæ constitute the *internal carotid arteries*. The ventral aortæ between the third and fourth aortic arches persist as the *common carotid arteries*. The descending aortæ in the same region are slender and eventually atrophy. The fourth aortic arch is largest, and on the left side will form the *aortic arch* of the adult. From the right fourth arch caudad, the right descending aorta is smaller than the left. Opposite the eighth segment, the two aortæ unite and continue caudally as the *median dorsal aorta*. The sixth aortic arches (cf. p. 100) are connected with the pulmonary trunk, and from them arise small *pulmonary arteries* to the lungs. Dorsal *intersegmental arteries* arise, six pairs from the de-

scending aortæ, others from the dorsal aorta. From the seventh pair, which arise just where the descending aortæ fuse, the *subclavian arteries* pass off to the upper limb buds and the *vertebral arteries* to the head. The latter are formed by a longitudinal anastomosis between the first seven pairs of intersegmental arteries on each side, after which the stems of the first six pairs atrophy.

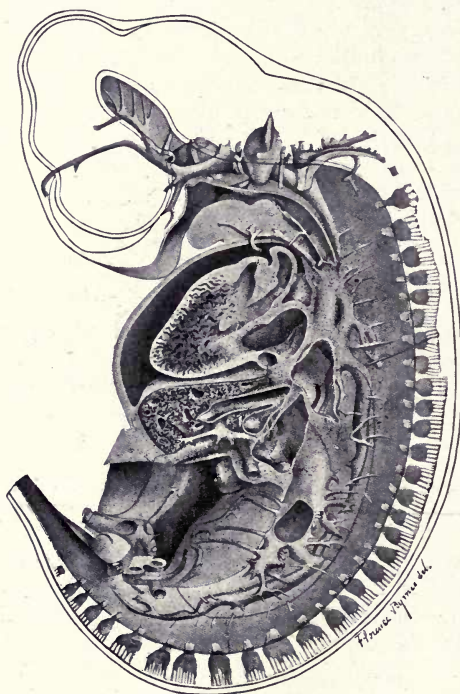


FIG. 126 A.—Reconstruction of a 12 mm. pig embryo, to show the veins and heart from the left side. For names of parts see Fig. 126 B on opposite page (F. T. Lewis). $\times 9$.

Ventro-lateral arteries from the dorsal aorta supply the mesonephros and genital ridge (Fig. 123). *Ventral arteries* form the *cæliac artery* to the stomach region, the *vitelline*, or *superior mesenteric artery*, to the small intestine, and the *inferior mesenteric artery* to the large intestine.

The umbilical arteries now arise laterally from secondary trunks which persist as the *common iliac arteries*.

The Veins.—The cardinal veins have been reconstructed by Lewis in a 12 mm. pig (Fig. 126). The veins of the head drain into the *anterior cardinal vein*, which becomes the *internal jugular vein* of the adult. After receiving the *external jugular veins* and the *subclavian veins* from the upper

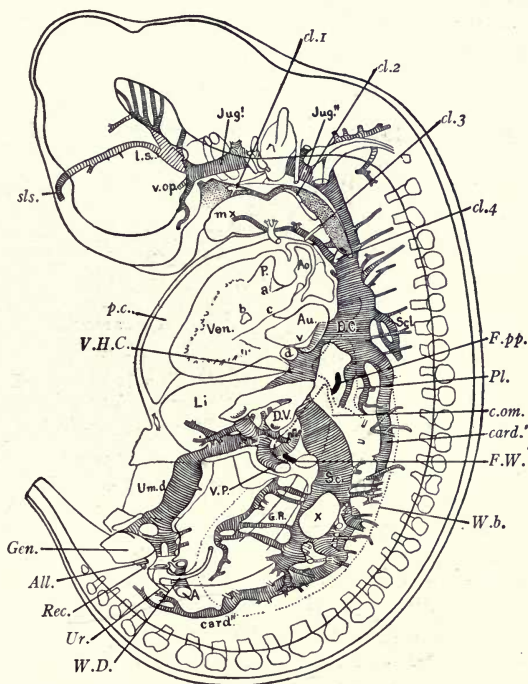


FIG. 126 B.—Reconstruction of a 12 mm. pig embryo, to show the veins from the left side (Lewis). $\times 9$. A., Umbilical artery; Ao., aorta; Au., right auricle (atrium); card.¹, card.², superior and inferior sections of posterior cardinal vein; d, left common cardinal vein; D.C., right common cardinal vein; D.V., ductus venosus; Jug.¹, Jug.², jugular or ant. cardinal vein; L., liver; L.s., anlage of lateral sinus; mx., transverse vein; P., pulmonary artery; Sc., subcardinal vein; Scl., subclavian vein; s.l.s., anlage of sup. longitudinal sinus; Um.d., right umbilical vein; Ven., right ventricle; V.H.C., common hepatic vein; V.op., ophthalmic vein; V.P., portal vein; X, anastomosis between the right and left subcardinal veins.

limb buds the anterior cardinals open into the *common cardinal veins* (ducts of Cuvier).

The *posterior cardinal veins* arise in the caudal region, course dorsal to the mesonephroi, and drain the mesonephric sinusoids. The sub-

cardinal veins anastomose just caudal to the origin of the superior mesenteric artery, and the posterior cardinals are interrupted at this level. The proximal portions of the posterior cardinals open into the common cardinal veins as in the 6 mm. embryo. Of the two *subcardinal veins*, the right has become very large through its connection with the right posterior cardinal vein and the common hepatic vein, and now forms the middle portion of the *inferior vena cava*. For the development of this vein, see Chapter IX.

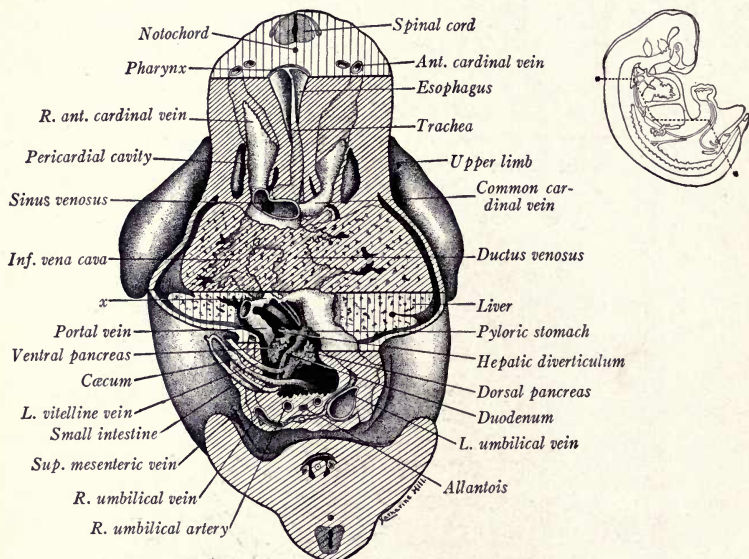


FIG. 127.—Reconstruction of a 10 mm. pig embryo, to show the umbilical and vitelline veins from the ventral side. *x*, indicates sinusoidal connection between left umbilical vein and portal vein. $\times 15$. In the small orientation figure (cf. Fig. 123) the various planes are indicated by broken lines—*.....*.

The *umbilical veins* (Figs. 126 and 127) anastomose in the umbilical cord, separate on entering the embryo, and course cephalad in the ventrolateral body wall of each side to the ventral lobe of the liver. The left vein is much the larger, and, after entering the liver, its course is to the right and dorsad. After connecting with the portal vein, it continues as the *ductus venosus* and joins the proximal end of the inferior vena cava. The smaller, right umbilical vein after entering the liver breaks up into sinusoids. It soon atrophies, while the left vein persists until after birth.

The Vitelline Veins.—Of these, a distal portion of the left and a proximal portion of the right are persistent. The left vitelline vein,

fused with the right, courses from the yolk sac cephalad of the intestinal loop. Near a dorsal anastomosis between the right and left vitelline veins, just caudal to the duct of the dorsal pancreas, the left receives the *superior mesenteric vein*, a new vessel arising in the mesentery of the intestinal loop. Cranial to its junction with the superior mesenteric vein, the left vitelline, with the dorsal anastomosis and the proximal portion of the right vitelline vein, forms the *portal vein*, which gives off branches to the hepatic sinusoids and connects with the left umbilical vein. For the development of the portal vein, see Chapter IX.

TRANSVERSE SECTIONS OF A TEN MM. PIG EMBRYO

Figures are shown of sections passing through the more important regions; these should be used for the identification of the organs. The level and plane of each section is indicated by guide lines on Fig. 128. The student should compare this with Figs. 118 and 123, and orient each

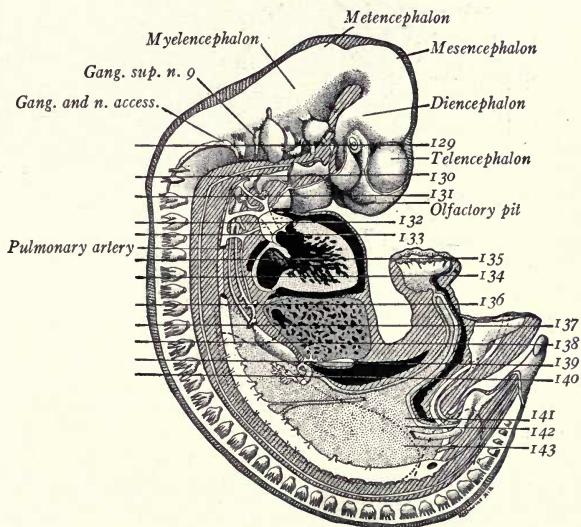


FIG. 128.—Reconstruction of a 10 mm. pig embryo, showing the chief organs of the left side. The numbered lines indicate the levels of transverse sections shown in the corresponding figures (129-143). For the names of the various structures not lettered see Fig. 123. $\times 8$.

section with reference to the embryo as a whole. To avoid repetition, most of the levels illustrated in the transverse sections of the 6 mm. pig are not represented in the 10 mm. series. For this reason, the former series will be found very instructive in supplementing the following descriptions.

Transverse Section through the Eyes and Otocysts (Fig. 129).—The brain is sectioned twice, lengthwise through the *myelencephalon*, transversely through the *fore-brain*. The brain wall shows differentiation into three layers: (1) an inner *ependymal layer*, densely cellular; (2) a middle *mantle layer* of nerve cells and fibers; (3) an outer *marginal layer*, chiefly fibrous. These same three layers are developed in the spinal cord. A thin, vascular layer differentiated from the mesenchyma surrounds the brain wall and is the anlage of the *pia mater*. The *myelencephalon* shows three neuromeres in this section. The telencephalon is represented by the paired *cerebral hemispheres*, their cavities, the

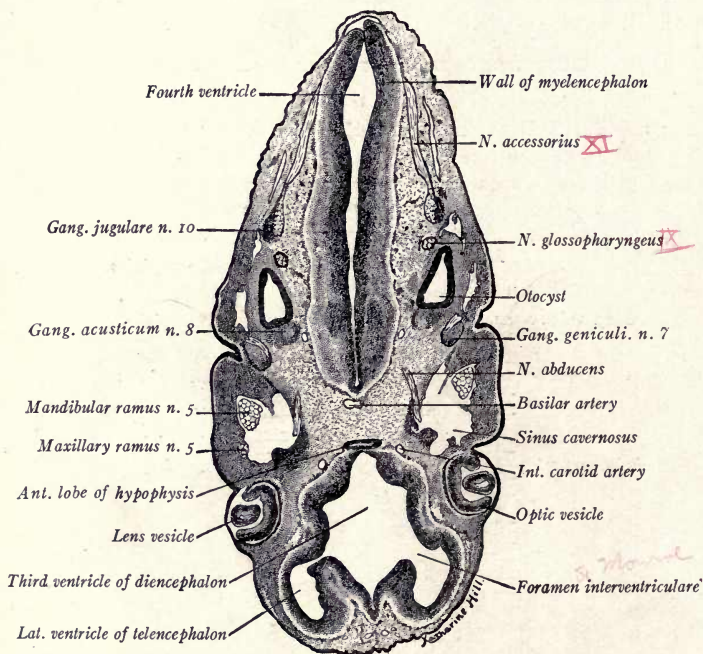


FIG. 129.—Transverse section through the eyes and otocysts of a 10 mm. pig embryo. $\times 22.5$.

lateral ventricles, connecting through the *interventricular foramina* with the *third ventricle* of the diencephalon. Close to the ventral wall of the diencephalon is a section of the anterior lobe of the hypophysis (*Rathke's pouch*) near which are the *internal carotid* and *basilar arteries*. Lateral to the diencephalon is the *optic cup* and *lens vesicle* of the eye, which are sectioned caudal to the optic stalk. The outer layer of the optic cup forms the thin *pigment layer*; the inner, thicker layer is the *nervous layer* of the retina. The *lens* is now a closed vesicle distinct from the overlying *corneal ectoderm*.

The large vascular spaces are the *cavernous sinuses*, which drain by way of the *vv. capitis laterales* into the internal jugular veins. Transverse sections may be seen of the *maxillary* and *mandibular branches* of the *n. trigeminus*; the *n. abducens* is sectioned longitudinally. The small *nn. oculomotorius* and *trochlearis* should be identified in sections

more cephalad in the series. Ventral to the otocyst are seen the *geniculate* and *acoustic ganglia* of the *nn. facialis* and *acusticus*. The wall of the *otocyst* forms a sharply defined epithelial layer. More cephalad in the series the *endolymph duct* lies median to the otocyst and connects with it. Dorsal to the otocyst the *n. glossopharyngeus* and the *jugular ganglion* of the *vagus* are cut transversely while the trunk of the *n. accessorius* is cut lengthwise.

Section through the First and Second Pharyngeal Pouches (Fig. 130).—The end of the head, with sections of the *telencephalon* and of the ends of the *olfactory pits*, is now

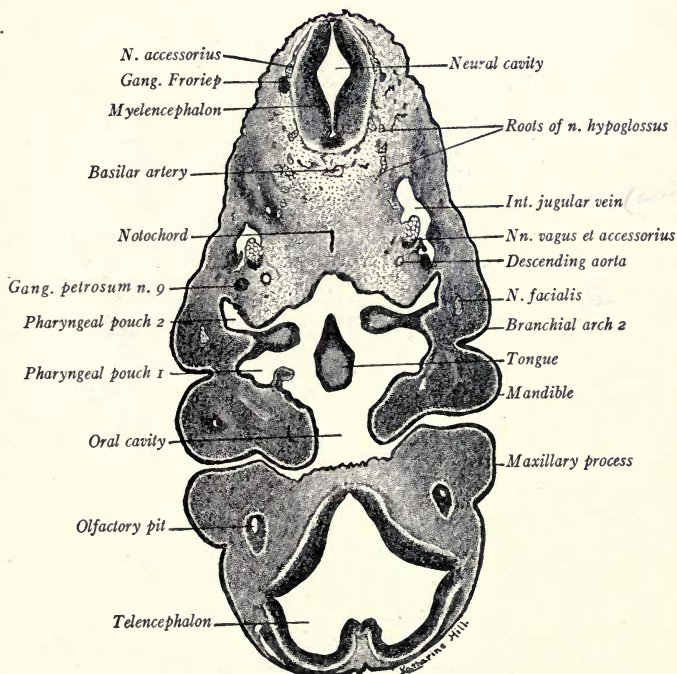


FIG. 130.—Transverse section through the first and second pharyngeal pouches of a 10 mm. pig embryo. $\times 22.5$.

distinct from the rest of the section. The *pharynx* shows portions of the *first* and *second pharyngeal pouches*. Opposite the first pouch externally is the *first branchial groove*. A section of the *tuberculum impar* of the tongue shows near the midplane in the pharyngeal cavity. The neural tube is sectioned dorsally at the level of *Froriep's ganglion*. Between the neural tube and the pharynx may be seen on each side the several root fascicles of the *n. hypoglossus*, the fibers of the *nn. vagus* and *accessorius*, and the *petrosal ganglion* of the *n. glossopharyngeus*. Mesial to the ganglia are the *descending aortae* and lateral to the vagus is the *internal jugular vein*.

Section through the Third Pharyngeal Pouches (Fig. 131).—The tip of the head is now small and shows on either side the deep *olfactory pits* lined with thickened *olfactory epithelium*. The *first, second, and third branchial arches* show on either side of the section, the third being slightly sunken in the *cervical sinus*. The dorsal diverticula of the *third pharyngeal pouches* extend toward the ectoderm of the third branchial groove. The ventral diverticula, or thymic anlagen, may be traced caudad in the series. The floor of the pharynx is sectioned through the *epiglottis*. Ventral to the pharynx are sections of the *third aortic arches* and the solid cords of the *thyroid gland*. Dorsally the section passes through the *spinal cord* and first pair of *cervical ganglia*. Between the cord and pharynx, named in

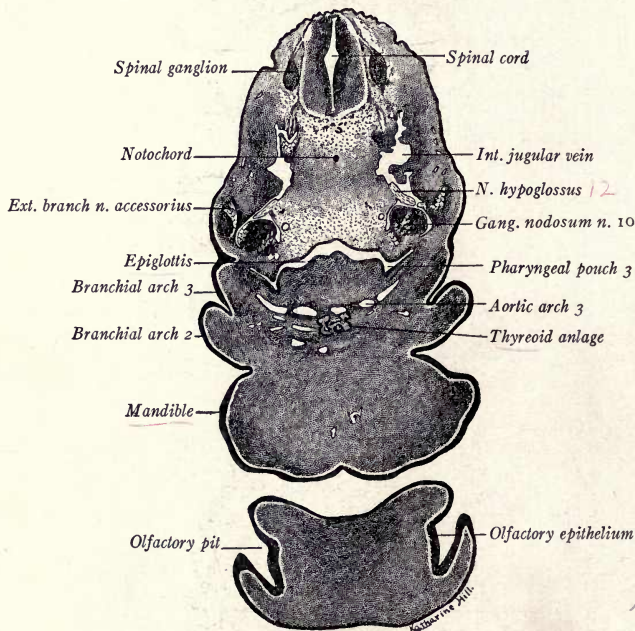


FIG. 131.—Transverse section through the third pharyngeal pouches of a 10 mm. pig embryo. $\times 22.5$.

order, are the *internal jugular veins*, the *hypoglossal nerve*, and the *nodose ganglion* of the *vagus*. Lateral to the ganglion is the external branch of the *n. accessorius*, and mesial to the ganglia are the small *descending aorta*.

Section through the Fourth Pharyngeal Pouches (Fig. 132).—This region is marked by the disappearance of the head and the appearance of the heart in the *pericardial cavity*. The tips of the *atria* are sectioned as they project on either side of the *bulbus cordis*. The bulbus is divided into the *aorta* and *pulmonary artery*, the latter connected with the right ventricle, which has spongy muscular walls. The *pharynx* is crescentic and continued laterally as the small *fourth pharyngeal pouches*. Into the mid-ventral wall of the pharynx

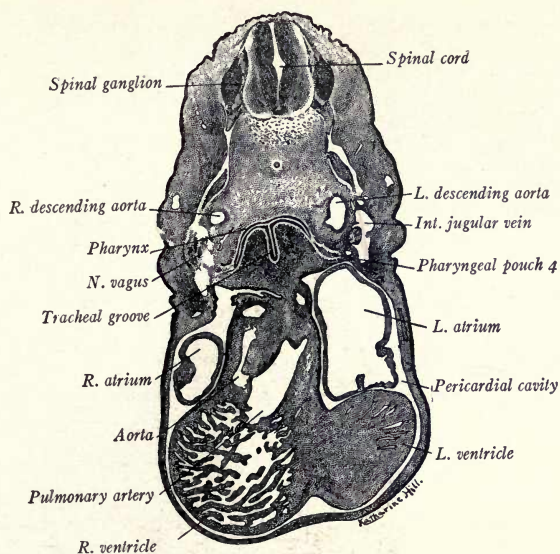


FIG. 132.—Transverse section through the fourth pharyngeal pouches of a 10 mm. pig embryo.
 $\times 22.5$.

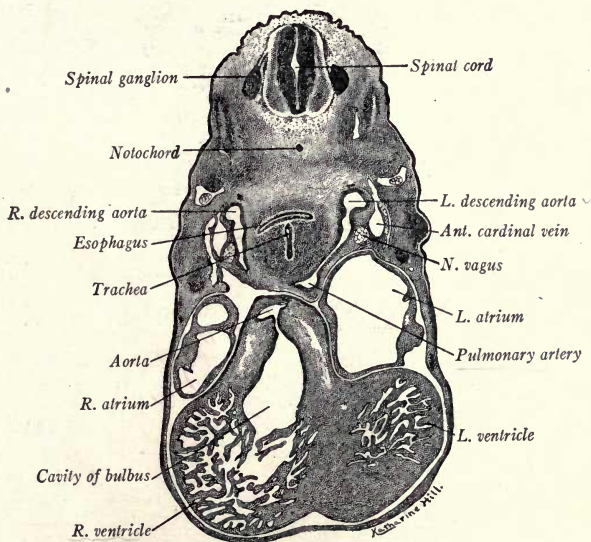


FIG. 133.—Transverse section through the sixth pair of aortic arches and bulbus cordis of a 10 mm. pig embryo. $\times 22.5$.

Section through the Foramen Ovale of the Heart (Fig. 135).—The level of this section is cranial to that of the previous figure and shows the *septum primum* interrupted dorsally to form the *foramen ovale*. Each atrium communicates with the ventricle of the same side through the *atrio-ventricular foramen*. Between these openings is the *endocardial cushion*, which in part forms the anlagen of the *tricuspid* and *bicuspid* valves. The atria are marked off externally from the ventricles by the *coronary sulcus*. Between the two ventricles is the *interventricular septum*. The ventricular walls are thick and spongy, forming a network of muscular cords, or *trabeculae*, surrounded by blood spaces, or *sinusoids*. The *trabeculae* are composed of muscle cells, which later become striated and constitute the *myocardium*. They are surrounded by an endothelial layer, the *endocardium*. The mammalian heart receives all its nourishment from the blood circulating in the sinusoids until later, when the *coronary vessels* of the heart wall are developed. The heart is surrounded by a layer of mesothelium, the *epicardium*, which is continuous with the *pericardial* mesothelium lining the body wall.

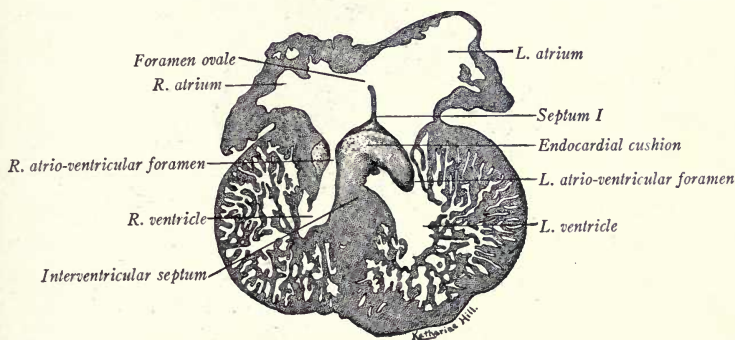


FIG. 135.—Transverse section through the foramen ovale of the heart in a 10 mm. pig embryo.
× 22.5.

Section through the Liver and Upper Limb Buds (Fig. 136).—The section is marked by the presence of the *upper limb buds*, the *liver*, and the bifurcation of the trachea to form the *primary bronchi* of the lungs. The *limb buds* are composed of dense, undifferentiated mesenchyme, surrounded by ectoderm which is thickened at their tips. The seventh pair of cervical ganglia and nerves are cut lengthwise, showing the spindle-shaped *ganglia* with the *dorsal root fibers* taking origin from their cells. The *ventral root fibers* arise from the ventral cells of the mantle layer and join the dorsal root to form the *nerve trunk*. On the right side a short *dorsal ramus* supplies the anlage of the dorsal muscle mass. The much larger *ventral ramus* unites with those of other nerves to form the *brachial plexus*.

The *descending aorta* have now fused and the seventh pair of dorsal *intersegmental arteries* arise from the *dorsal aorta*. From these intersegmental arteries the *subclavian arteries* are given off two sections caudad in the series. Lateral to the aorta are the *posterior cardinal veins*. The esophagus, ventral to the aorta, shows a very small lumen, while that of the trachea is large and continued into the *bronchi* on either side. Adjacent to the esophagus are the cut *vagus* nerves. The *lung anlagen* project laterally into the crescentic *pleural cavities*, of which the left is separated from the peritoneal cavity by the *sep-*

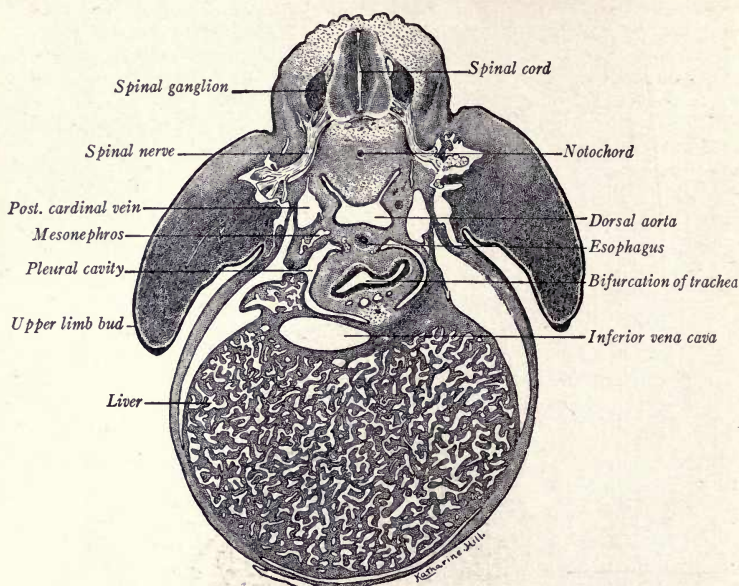


FIG. 136.—Transverse section through the liver and upper limb buds of a 10 mm. pig embryo, at the level of the bifurcation of the trachea. $\times 22.5$.

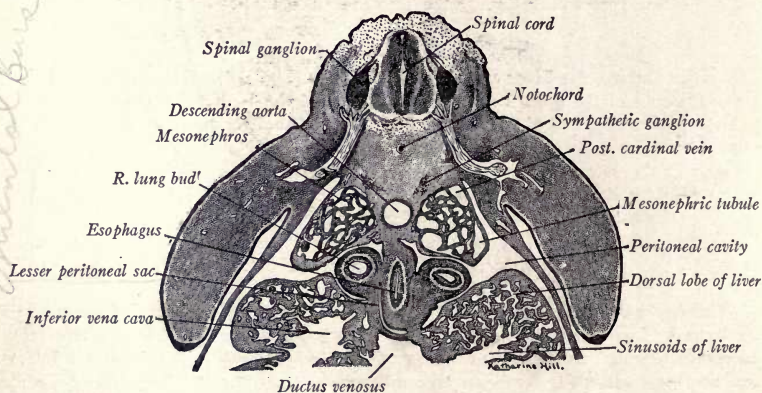


FIG. 137.—Dorsal half of a transverse section through the lung buds, cranial to the stomach, in a 10 mm. pig embryo. $\times 22.5$.

tum transversum. The liver, with its fine network of trabeculae and sinusoids, is large and nearly fills the peritoneal, or abdominal cavity. The *liver cords* are composed of liver cells surrounded by the endothelium of the sinusoids. Red blood cells are developed in the liver at this stage. The large vein, from the liver to the heart, penetrating the septum transversum is the proximal portion of the *inferior vena cava*, originally the right vitelline vein. Ventral to the bronchi may be seen sections of the *pulmonary veins*.

Section through Lung Buds, Cranial to Stomach (Fig. 137).—The *lungs* are sectioned through their caudal ends and the esophagus is just beginning to dilate into the *stomach*. On either side of the circular dorsal aorta are the *mesonephroi*, while dorso-laterally are *sympathetic ganglia*. The pleural cavities now communicate freely on both sides with the peritoneal cavity. A section of the *lesser peritoneal sac* appears as a crescent-shaped slit at the right of the esophagus. In the right dorsal lobe of the liver is located the *inferior vena cava*. Near the median plane ventral to the lesser sac is the large *ductus venosus*.

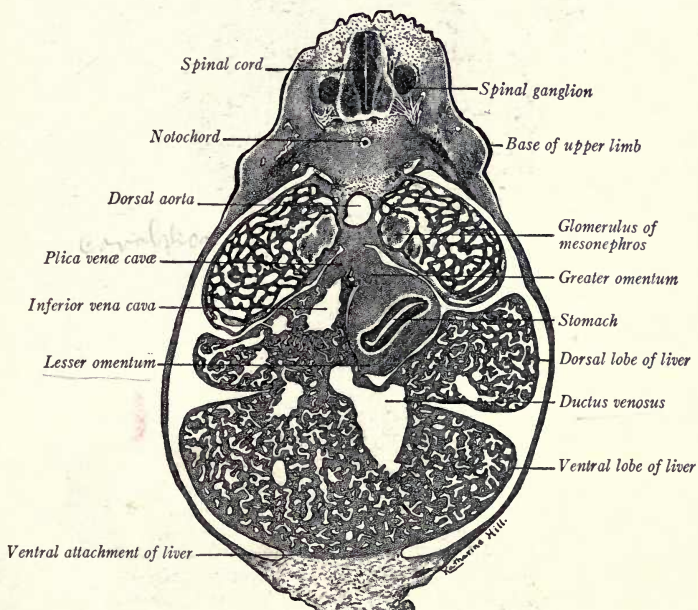


FIG. 138.—Transverse section through the stomach and liver of a 10 mm. pig embryo. $\times 22.5$.

Section through the Stomach and Liver (Fig. 138).—Prominent in the body cavity are the *mesonephroi* and liver lobes. The mesonephroi show sections of coiled tubules lined with cuboidal epithelium. *Glomeruli* of the renal corpuscles are median in position and develop as knots of small arteries which grow into the ends of the tubules. The thickened epithelium along the median and ventral surface of the mesonephros is the anlage of the *genital gland*. The body wall is thin and lined with mesothelium continuous with that which covers the mesenteries and organs. The mesothelial layer becomes the epithelium of the adult *peritoneum*, *mesenteries*, and *serous layer* of the viscera. The *stomach* lies on

the left side and is attached dorsally by the *greater omentum*, ventrally to the liver by the *lesser omentum*. The right dorsal lobe of the liver is attached dorsally to the right of the great omentum. In the liver, ventral to this attachment, courses the *inferior vena cava* and the attachment forms the *plica venæ cavæ*. Between the attachments of the stomach and liver, and to the right of the stomach, is the *lesser peritoneal sac*. In the liver, to the left of the midplane is the *ductus venosus*, sectioned just at the point where it receives the *left umbilical vein* and a branch from the *portal vein*. The ventral attachment of the liver later becomes the *falciform ligament*.

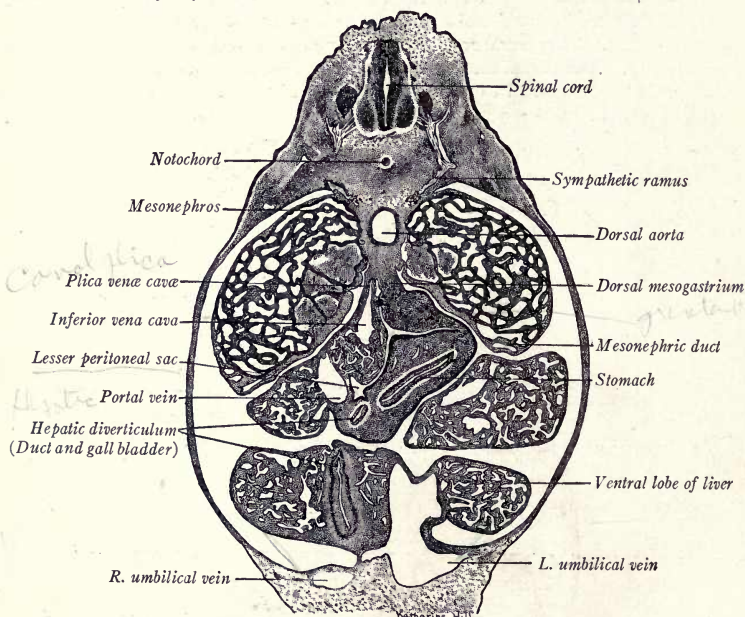


FIG. 139.—Transverse section through the hepatic diverticulum of a 10 mm. pig embryo. $\times 22.5$.

Section through the Hepatic Diverticulum (Fig. 139).—The section passes through the pyloric end of the stomach and duodenum, near the attachment of the hepatic diverticulum. The greater omentum of the stomach is larger than in the previous section and to its right, in the plica venæ cavæ, lies the *inferior vena cava*. Ventral to the inferior vena cava is a section of the portal vein. The ventral and dorsal lobes of the liver are now separate, and in the right ventral lobe is embedded the saccular end of the *hepatic diverticulum* which forms the *gall bladder*. To the right of the stomach, the diverticulum is sectioned again just as it enters the *duodenum*. Ventrally, the *left umbilical vein* is entering the left ventral lobe of the liver. It is much larger than the right vein, which still courses in the body wall. On the left side of the embryo the *spinal nerve* shows in addition to its dorsal and ventral rami a *sympathetic ramus*, the fibers of which pass to a cluster of ganglion cells located dorso-lateral to the aorta. These cells form one of a pair of *sympathetic ganglia* and are derived from a spinal ganglion.

Section through the Pancreatic Anlages (Fig. 140).—The lesser peritoneal sac just above the level of this section has opened into the peritoneal cavity through the *epiploic foramen* (of Winslow). The *mesonephric ducts* are now prominent ventrally in the mesonephroi. The duct of the *dorsal pancreas* is sectioned tangentially at the point where it

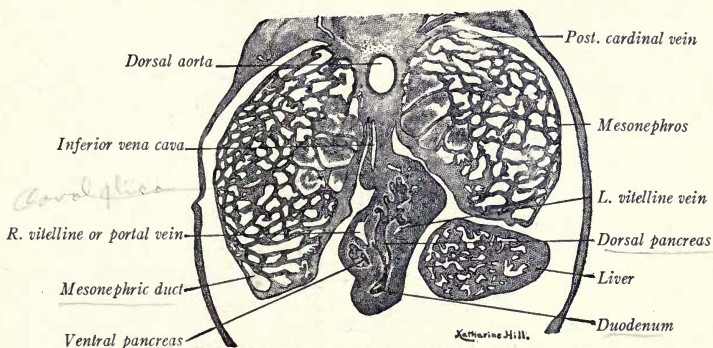


FIG. 140.—Portion of a transverse section through the pancreatic anlages of a 10 mm. pig embryo. $\times 22.5$.

takes origin from the duodenum. From the duct the lobulated gland may be traced dorsad in the mesentery. To the right of the dorsal pancreatic duct is a section of the *ventral pancreas*, which may be traced cephalad in the series to its origin from the *hepatic diverticulum*. Dorsal to the ventral pancreas is a section of the *portal vein*. The inferior vena cava appears as a vertical slit in the dorsal mesentery.

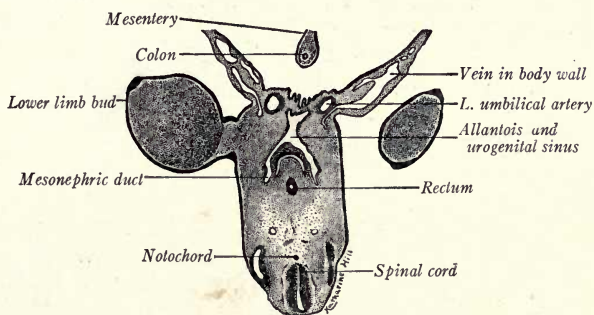


FIG. 141.—Transverse section through the urogenital sinus and rectum of a 10 mm. pig embryo. $\times 22.5$.

Section through the Urogenital Sinus and Lower Limb Buds (Fig. 141).—The figure shows only the caudal end of a section, in the dorsal portion of which the mesonephroi were sectioned at the level of the *subcardinal anastomosis*. A portion of the *mesentery* is shown with a section of the *colon*. In the body wall are veins that drain into the umbilical veins, and on each side are the *umbilical arteries*, just entering the body from the umbili-

cal cord. Between them, in sections cranial to this, the *allantoic stalk* is located. Here it has opened into the crescentic *urogenital sinus*. Dorsal to the urogenital sinus (dorsal now being at the bottom of the figure, owing to the curvature of the caudal region) is a section of the *rectum*, separated from the sinus by a curved prolongation of the *cœlom*. From the ends of the urogenital sinus, as we trace cephalad in the embryo (*downward* in the series), are given off the *mesonephric ducts*.

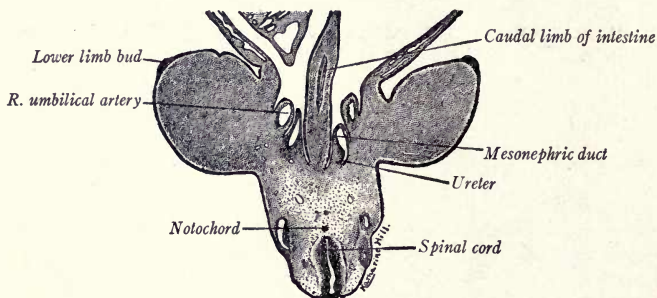


FIG. 142.—Transverse section of a 10 mm. embryo passing through the lower limb buds at the level of the openings of the ureters into the mesonephric ducts. $\times 22.5$.

Section through the Mesonephric Ducts at the Opening of the Ureter (Fig. 142). The section cuts through both lower limb buds near their middle. Mesial to their bases are the *umbilical arteries*, which lie lateral to the *mesonephric ducts*. From the dorsal wall of the left mesonephric duct is given off the *ureter*, or duct of the metanephros. Tracing the sections down in the series, both ureters appear as minute tubes in transverse section. They soon dilate to form the *pelvis* of the kidney at the level of Fig. 143. Note the undifferentiated mesenchyme of the *lower limb buds* and their thickened ectodermal tips.

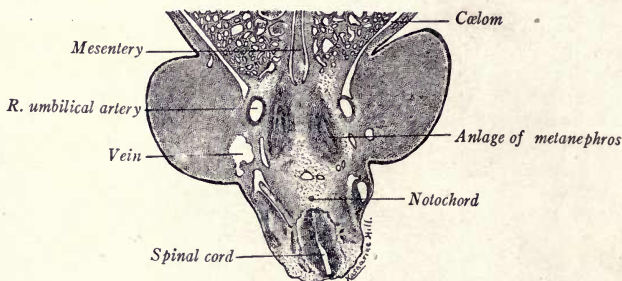


FIG. 143.—Transverse section through the anlagen of the metanephroi in a 10 mm. pig embryo. $\times 22.5$.

Section through the Metanephroi and Umbilical Arteries (Fig. 143).—The section passes caudal to the mesonephric ducts, which curve along the ventral surfaces of the mesonephroi (Fig. 124). The umbilical arteries course lateral to the metanephroi; these consist merely of the thickened epithelium of the pelvis surrounded by a layer of condensed mesenchyma, the *nephrogenic tissue*.

CHAPTER VI

THE DISSECTION OF PIG EMBRYOS: DEVELOPMENT OF THE FACE, PALATE, TONGUE, SALIVARY GLANDS AND TEETH

THE DISSECTION OF PIG EMBRYOS

As the average student will not have time to study series of embryos sectioned in different planes, dissections may be used for showing the form and relations of the organs. Cleared embryos mounted whole are instructive, but show the structures superimposed and are apt to confuse the student. Pig embryos 10 mm. or more in length may be easily dissected, mounted as opaque objects, and used for several years. Success in dissecting such small embryos depends: (1) on the *fixation and hardening* of the material employed; (2) on starting the dissection with a *clean cut in the right plane*; (3) on a knowledge of the anatomy of the parts to be dissected.

Fixation and Hardening of Material.—Embryos fixed in Zenker's fluid have given the best results. They should then be so hardened in 95 per cent alcohol that the more diffuse mesenchyma will readily separate from the surfaces of the various organs, yet the organs must not be so brittle that they will crumble and break. Embryos well hardened and then kept for two weeks in 80 per cent alcohol usually dissect well. Old material is usually too brittle; that just fixed and hardened may prove too soft. As a test, determine whether the mesenchyma separates readily from the cervical ganglia and their roots.

Dissecting instruments include a binocular dissecting microscope, a sharp safety razor blade, large, curved, blunt-pointed dissecting needles, pairs of small, sharp-pointed forceps, and straight dissecting needles, small and large.

Methods of Dissection.—In general, it is best to begin the dissection with a clean, smooth cut made by a single stroke with the safety razor blade, which should be flooded with 80 per cent alcohol. The section is made free hand, holding the embryo, protected by a fold of absorbent cotton, between the thumb and index finger. Having made preliminary cuts in this way, the embryo may be affixed with thin celloidin to a cover glass and immersed in a watch glass containing alcohol. We prefer not to affix the embryo, as the celloidin used for this purpose may interfere with the dissection. Instead, a cut is made parallel to the plane of the dissection so that the embryo, resting in the watch glass upon this flat surface, will be in a fairly stable position. It may thus be held in any convenient position by resting the convex surface of a curved, blunt dissecting needle upon some part not easily injured. The dissection is then carried on under the binocular microscope, using the fine pointed forceps, dissecting needles, and a small pipette to wash away fragments of tissue.

Whole Embryos.—For the study of the exterior, whole embryos may be affixed with celloidin to the bottoms of watch glasses which may be stacked in wide-mouthed jars of 80 per cent alcohol. The specimens may thus be used several years at a saving of both time and material. Preliminary treatment consists in immersion in 95 per cent alcohol one hour, in ether and absolute alcohol at least thirty minutes, in thin celloidin one hour or more. Pour enough thin celloidin into a Syracuse watch glass to cover its bottom, and immerse in this a circle of black mat paper, first wet with ether and absolute alcohol. Pour

off any surplus celloidin, mount embryo in desired position and immerse watch glass in 80 per cent alcohol, in which the specimen may be kept indefinitely. Embryos may also be mounted in gelatin-formalin solution in small, sealed glass jars.

Lateral Dissections of the Viscera.—Dissections like those shown in Figs. 144 and 145 may easily be prepared in less than an hour, and make valuable demonstration and

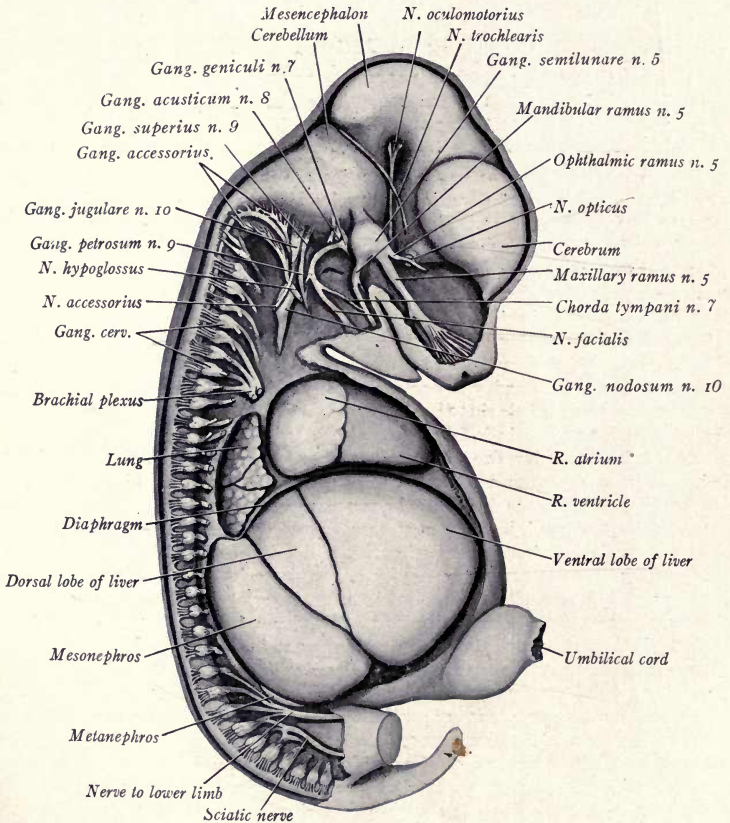


FIG. 144.—Lateral dissection of an 18 mm. pig embryo, showing the nervous system and viscera from the right side. $\times 8$.

laboratory specimens. Skill is required to demonstrate most of the cerebral nerves, but the central nervous system, cerebral and spinal ganglia, and viscera may easily be exposed. Starting dorsally, make a sagittal section of the embryo slightly to one side of the median line and avoiding the umbilical cord ventrally. With the embryo resting on the flat, sectioned surface, begin at the cervical flexure, and with fine forceps grasp the ectoderm and dural anlage at its cut edge, separate it from the neural tube and pia mater, and strip it

off ventralwards, exposing the myelencephalon and cervical portion of the cord. As the mesenchyma is pulled away, the ganglia and roots of the cerebral nerves will be exposed. The mesenchyma between the ganglia and along the nerves may be removed with the end of a small blunt needle. Care must be exercised in working over the mesencephalon and

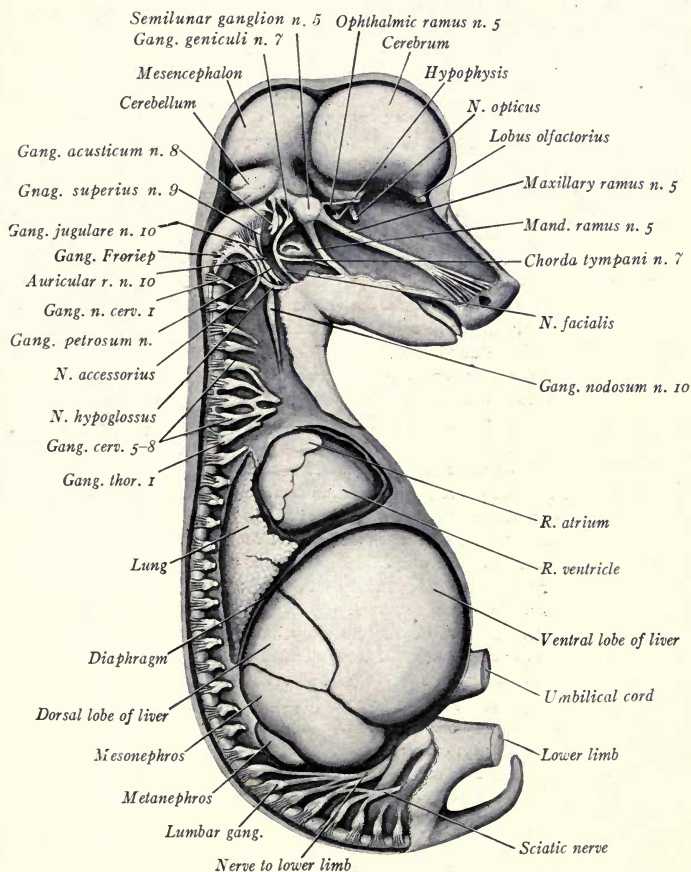


FIG. 145.—Lateral dissection of a 35 mm. pig embryo, to show the nervous system and viscera from the right side. $\times 4$.

telencephalon of the brain not to injure the brain wall, which may be brittle. By starting with a clean dissection dorsally and gradually working ventrad, the more important organs may be laid bare without injury. The beginner should compare his specimen with the dissections figured and also previously study the reconstructions of Thyng (1911) and Lewis (1903).

Lateral dissections of embryos 18 mm. and 35 mm. long show infinitely better than sections the form and relations of the organs, their relative growth, and their change of position (Figs. 144 and 145). Compare the organs of 6, 10, 18, and 35 mm. embryos and note the rapid growth of the viscera (see Figs. 95 and 120). Hand-in-hand with the increased size of the viscera goes the diminution of the *dorsal* and *cervical flexures*. In the brain, note the increased size of the *cerebral hemispheres* of the telencephalon and the presence of the olfactory lobe of the *rhinencephalon*. The *cerebellum* also becomes prominent and a ventral flexure in the region of the pons, the *pontine flexure*, is more marked. The brain grows relatively faster than the spinal cord, and, by the elongation of their dorsal roots, the spinal ganglia are carried ventral to the cord. The body of the embryo also grows faster than the spinal cord, so that the spinal nerves, at first directed at right angles to the cord, course obliquely caudad in the lumbo-sacral region.

Median Sagittal Dissections (Figs. 146 and 147).—Preliminary to the dissection, a cut is made dorsally as near as possible to the median sagittal plane. Beginning caudally at the mid-dorsal line, an incision is started which extends in depth through the neural tube and the anlagen of the vertebræ. This incision is carried to the cervical flexure, cranial to which point the head and brain are halved as accurately as possible. The blade is then carried ventrally and caudally, cutting through the heart and liver to the right of the *midplane* and *umbilical cord* until the starting point is reached. A parasagittal section is next made well to the left of the median sagittal plane and the sectioned portion is removed, leaving on the left side of the embryo a plane surface. With the embryo resting upon this flat surface, the dissection is begun by removing with forceps the right half of the head. In pulling this away caudalwards, half of the dorsal body wall, the whole of the lateral body wall, and the parts of the heart and liver lying to the right of the midplane will be removed, leaving the other structures intact. If the plane of section was accurate, the brain and spinal cord will be halved in the median sagittal plane. Wash out the cavities of the brain with a pipette and its internal structure may be seen. Dissect away the mesenchyma between the esophagus and trachea and expose the *lung*. Remove the right mesonephros, leaving the proximal part of its duct attached to the urogenital sinus. The right dorsal lobe of the liver will overlie the stomach and pancreas. Pick it away with forceps and expose these organs. Dissect away the caudal portion of the liver until the *hepatic diverticulum* is laid bare. It is whitish in color and may thus be distinguished from the brownish liver. Beginning at the base of the umbilical cord, carefully pull away its right wall with forceps, thus exposing the *intestinal loop* and its attachment to the yolk stalk. If the umbilical artery is removed in the caudal portion of the umbilical cord, the *allantoic stalk* may be dissected out. To see the anlage of the *genital gland*, break through and remove a part of the mesentery, exposing the mesial surface of the *left* mesonephros and the genital fold. The dissection of the metanephros and ureter is difficult in small embryos. In 10 to 12 mm. embryos, the umbilical artery, just after it leaves the aorta, passes lateral to the metanephros and thus locates it. By working carefully with fine needles, the surface of the *metanephros* may be laid bare and the delicate *ureter* may be traced to the base of the mesonephric duct. The extent of the *dorsal aorta* may also be seen by removing the surrounding mesenchyma. With a few trials, such dissections are made in a short time; they are invaluable in giving an idea of the form, positions, and relations of the different organs. By comparing the early (Figs. 96 and 122) with the later stages (Figs. 146 and 147) a number of interesting points may be noted.

In the brain, the *corpus striatum* develops in the floor of the cerebral hemispheres. The *interventricular foramen* is narrowed to a slit. In the roof of the diencephalon appears the anlage of the *epiphysis*, or *pineal gland*, and the *chorioid plexus* of the third ventricle.

This extends into the lateral ventricles as the *lateral chorioid plexus*. The dorso-lateral wall of the diencephalon thickens to form the *thalamus*, and the third ventricle is narrowed to a vertical slit. The increased size of the *cerebellum* has been noted. Into the thin dorsal

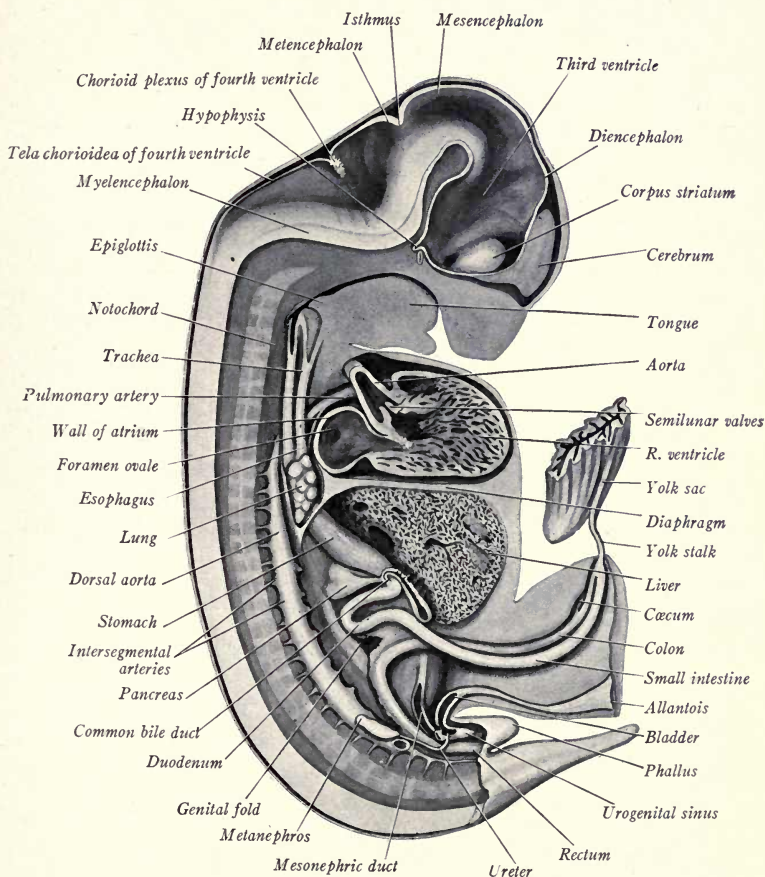


FIG. 146.—Median sagittal dissection of an 18 mm. pig embryo, showing the brain in section and the viscera in position. $\times 8$.

wall of the myelencephalon grows the network of vessels that forms the *chorioid plexus* of the *fourth ventricle*, which is now spread out laterally and flattened dorso-ventrally. About the notochord, mesenchymal anlagen which form the centra of the *vertebræ* are prominent.

Turning to the alimentary tract, observe that the primitive mouth cavity is now divided by the palatine folds into the upper *nasal passages* and lower *oral cavity*. In the lateral walls of the nasal passages develop the anlagen of the *turbinate bones*. On the floor of the mouth and pharynx, the *tongue* and *epiglottis* become more prominent. The *trachea* and *esophagus* elongate and the lungs lie more and more caudad. The dorsal portion of

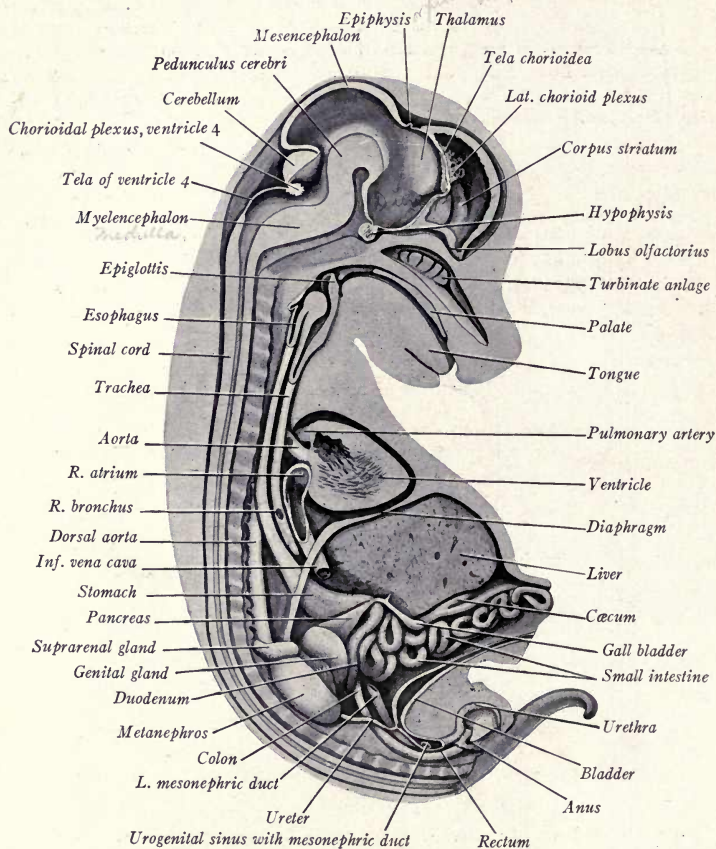


FIG. 147.—Median sagittal dissection of a 35 mm. embryo. $\times 4$.

the *septum transversum*, the anlage of a portion of the diaphragm, is thus carried caudad, and although originally, when traced from the dorsal body wall, it was directed caudad and ventrad, now it curves cephalad and ventrad, bulging cephalad into the thorax. The proximal limb of the *intestinal loop* elongates rapidly, and, beginning with the duodenum, becomes flexed and coiled in a characteristic manner. The distal limb of the intestinal

loop is not coiled, but its diverticulum, the *cæcum*, is more marked. Caudally, the *rectum*, or straight gut, has completely separated from the urogenital sinus and opens to the exterior through the *anus*.

Of the urogenital organs, the *genital folds* have become the prominent *genital glands*, attached to the median surfaces of the *mesonephroi*. The *metanephroi* have increased rapidly in size and have shifted cephalad. Proximal to the allantoic stalk the adjacent portion of the urogenital sinus has dilated to form the *bladder*. As the urogenital sinus grows, it takes up into its wall the proximal ends of the mesonephric ducts, so that these and the ureters have separate openings into the sinus. Owing to the unequal growth of the sinus wall, the ureters open near the base of the bladder, the mesonephric ducts more caudally into the *urethra*. The phallus now forms the *penis* of the male or the *clitoris* of the female. Cranial to the metanephros, a new organ, the *suprarenal gland*, has developed. This is a ductless gland and is much larger in human embryos.

The *heart*, as may be seen by comparing Figs. 96 and 147, although at first pressed against the tip of the head, shifts caudally, until in the 35 mm. embryo, it lies in the thorax opposite the first five thoracic nerves. Later it shifts even further caudad. The same is true of the other internal organs, the metanephros excepted. As the chief blood vessels are connected with the heart and viscera, profound changes in the positions of the vessels are thus brought about, for the vessels must shift their positions with the organs which they supply.

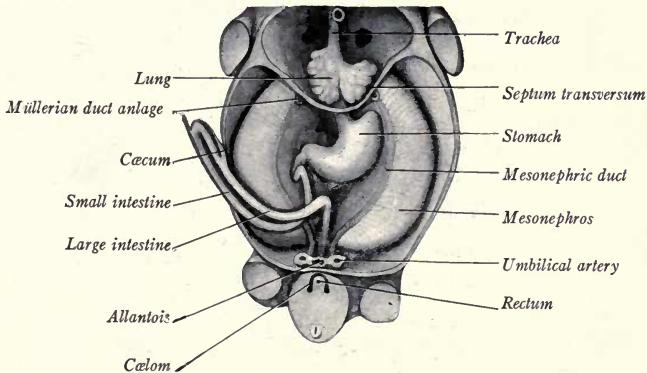


FIG. 148.—Ventral dissection of a 15 mm. pig embryo, showing lungs, digestive canal and mesonephroi. The ventral body wall, heart and liver have been removed and the limb buds cut across. $\times 6$.

Ventral Dissections.—Ventral dissections of the viscera are very easily made. With the safety razor blade, start a cut in a coronal plane through the caudal end of the embryo and the lower limb buds (Fig. 148). Extend this cut laterad and cephalad through the body wall and the upper limb bud. The head may be cut away in the same plane of section, and the cut continued through the body wall and upper limb bud of the opposite side back caudally to the starting point. Section the embryo in a coronal plane, parallel with the first section and near the back, so that the embryo will rest upon the flattened surface. With forceps, now remove the ventral body wall. By tearing open the wall of the umbilical cord along one side, it may be removed, leaving the intestinal loop intact. Pull away the

heart, noting its external structure. The liver may also be removed, leaving the stomach and intestine uninjured. A portion of the septum transversum covering the lungs may be carefully stripped away and the lungs thus laid bare.

Dissections made in this way show the trachea and lungs, the esophagus, stomach and dorsal attachment of the septum transversum, the course of the intestinal canal, and also the mesonephroi and their ducts. Favorable sections through the caudal end of the body may show the urogenital sinus, rectum, and sections of the umbilical arteries and allantois (Figs. 97, 124 and 148). In late stages, by removing the digestive organs, the urogenital ducts and glands are beautifully demonstrated (Figs. 223 and 224).

DEVELOPMENT OF THE FACE

The heads of pig embryos have long been used for the study of the development of the face. The heads should be removed by passing the razor blade between the heart and the adjacent surface of the head, thus severing the neck. Next cut away the dorsal part

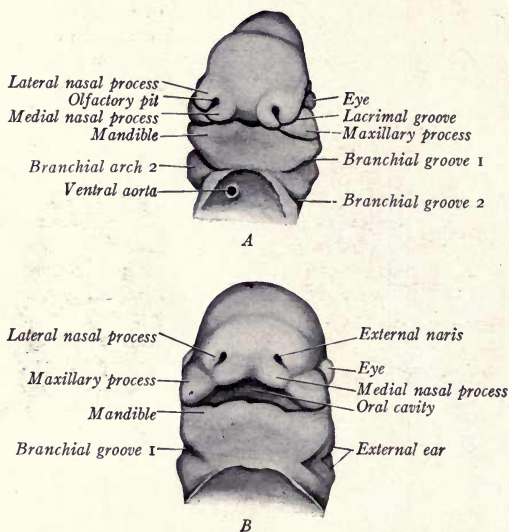


FIG. 149.—Two stages showing the development of the face in pig embryos. $\times 7$. A, 12 mm.; B, 14 mm.

of the head by a section parallel to the ventral surface, the razor blade passing dorsal to the branchial clefts and eyes. Mount, ventral side up, three stages from embryos 6, 12, and 14 mm. long, as shown in Figs. 97 and 149.

In the early stages (Figs. 97 and 124), the four, paired branchial arches and grooves are seen. Each first arch has already bifurcated into a *maxillary* and *mandibular process*. The third and fourth arches soon sink into the cervical sinus, while the mandibular processes of the first arch are

fused early to form the *lower jaw*. Laterally, the frontal process of the head is early divided into *lateral* and *median nasal processes* by the development of the olfactory pits. These processes are distinct and most prominent at 12 mm. (Fig. 149 A). Soon, in 13 to 14 mm. embryos, the median nasal processes fuse with the maxillary processes of the first arch and constitute the *upper jaw* (Fig. 149 B). The lateral nasal processes fuse with

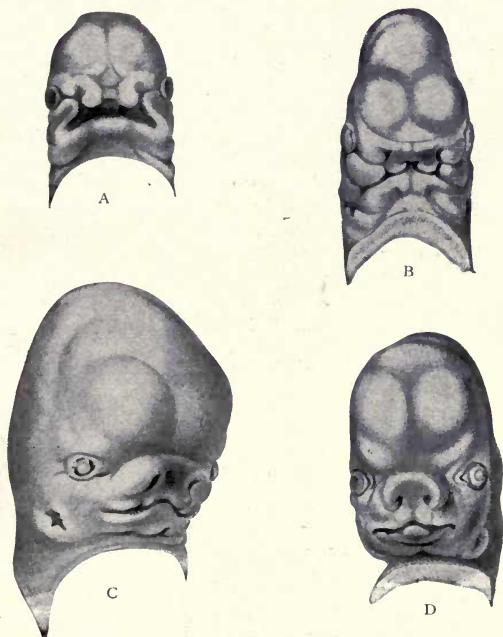


FIG. 150.—Development of the face of the human embryo (His). A, Embryo of 8 mm. ($\times 7.5$); the median frontal process differentiating into median nasal processes, or processes globulares, toward which the maxillary processes of the first branchial arch are extending. B, Embryo of 13.7 mm. ($\times 5$); the globular, lateral nasal and maxillary processes are in apposition; the primitive naris is now better defined. C, Embryo of 17 mm. ($\times 5$); immediate boundaries of mouth are more definite and the nasal orifices are partly formed, the external ear appearing. D, Embryo of nearly eight weeks ($\times 5$).

the maxillary processes and form the *cheeks*, the lateral part of the *lip*, and the *alæ* of the nose. Later, the median nasal processes unite and become the median part of the upper lip. Meanwhile, the mesial remainder of the original frontal process (Fig. 149 A) is compressed and becomes the *septum* and *dorsum* of the nose. The development of the olfactory organ will be traced on p. 371.

The early development of the face is practically the same in human embryos (Figs. 150 and 370). In embryos of 8 mm. the lateral and median nasal processes have formed. The maxillary processes next fuse with the nasal processes, after which the median nasal processes unite. Coincident with these changes the mandibular processes fuse and from them a median projection is developed which forms the anlage of the chin.

The *external ear* is developed around the first branchial groove by the appearance of small tubercles which form the *auricle*. The groove itself becomes the *external auditory meatus* and the *concha* of the ear. (For the development of the external ear see Chapter XIII.)

Epithelial ingrowths begin to separate the lips from the jaws at the fifth week (Fig. 159). The inner edges of the lips at birth bear numerous villousities. The line of fusion of the median nasal processes is evident in the adult as the *philtrum*.

Anomalies.—A common facial defect is *hare lip*. This is usually unilateral and on the left side. It may involve both lip and maxilla. Hare lip is attributed to the failure to fuse of the median nasal and maxillary processes (Kölliker), or the lateral and median nasal processes (Albrecht).

DEVELOPMENT OF THE PALATE

This may be studied advantageously in pig embryos of two stages: (a) 20 to 25 mm. long; (b) 28 to 35 mm. long. Dissections are made by carrying a shallow incision from the anlage of the mouth back to the external ear on each side (Fig. 152). The incisions are then continued through the neck in a plane parallel to the hard palate. Before mounting the preparation, remove the top of the head by a section cutting through the eyes and nostrils, parallel to the first plane of section. Transverse sections through the snout may also be prepared to show the positions of tongue and palatine folds before and after the fusion of the latter (Fig. 151).

In pig embryos of 20 to 25 mm. the jaws are close together and the mandible usually rests against the breast. Shelf-like folds of the maxillæ, the *lateral palatine processes*, are separated by the tongue and are directed ventrad (Figs. 151 A and 152 A). The median nasal processes also give rise to a single, heart-shaped structure, the *median palatine process* (Fig. 152). In embryos of 26 to 28 mm. the mandible drops, owing to growth changes, and the tongue is withdrawn from between the palatine processes (Fig. 151 B). With the withdrawal of the tongue the palatine folds bend upward to the horizontal plane, approach each other and fuse to form the *palate*, thus cutting off the nasal passages from the primitive oral cavity (Fig. 152 B). The primitive choanæ (cf. Fig. 153), formed by rupture of the membrane separating the olfactory pits from the oral cavity, now lead into the nasal passages, which in turn communicate with the pharynx by secondary, permanent *choanæ*. At the point in the median line where the lateral and median palatine processes meet, fusion is not complete, leaving

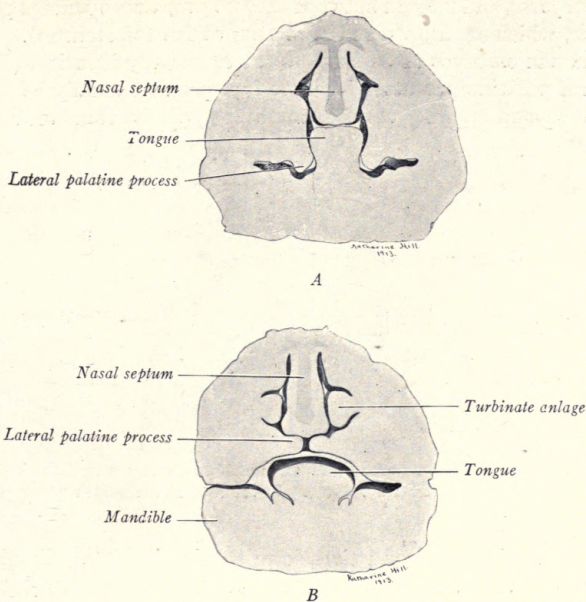


FIG. 151.—Sections through the jaws of pig embryos, to show the development of the palate.
 $\times 8$. A, 22 mm.; B, 34 mm.

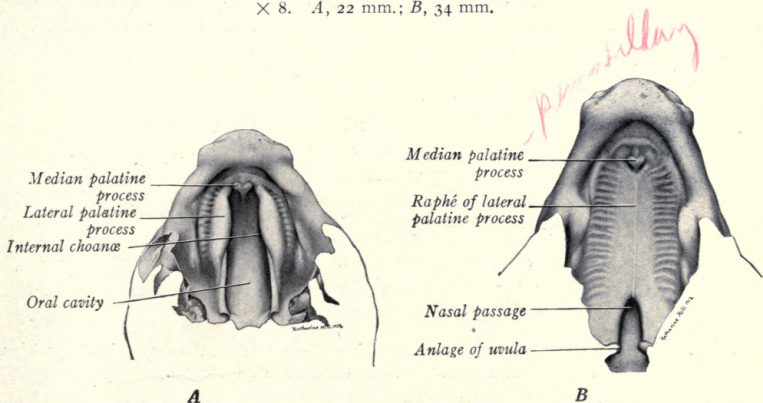


FIG. 152.—Dissections to show the development of the hard palate in pig embryos. $\times 5$.
 A, The upper jaw and palatine processes of a 22 mm. embryo in ventral view; B, Fusion of palatine processes in a 35 mm. embryo.

the *incisive fossa*, and laterad between the two processes openings persist for some time, which are known as the *incisive canals* (of Stenson).

In human embryos these changes are essentially identical (Fig. 153). The lateral palatine processes begin to fuse cranio-caudally at about the end of the second month. At the same time, *palatine bones* first appear in

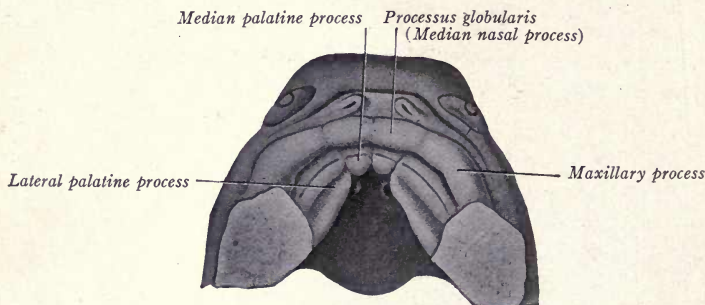


FIG. 153.—The roof of the mouth of a human embryo about ten weeks old, showing the development of the palate (after His). $\times 9$. In the roof of the mouth are the openings of the primitive choanae.

the lateral palatine folds and thus form the *hard palate*. Caudally, the bones do not develop, and this portion of the folds forms the *soft palate* and the *uvula* (Fig. 152). The unfused backward prolongations of the palatine folds give rise to the *pharyngo-palatine arches*, which are taken in adult anatomy as the boundary line between the oral cavity proper and the pharynx.

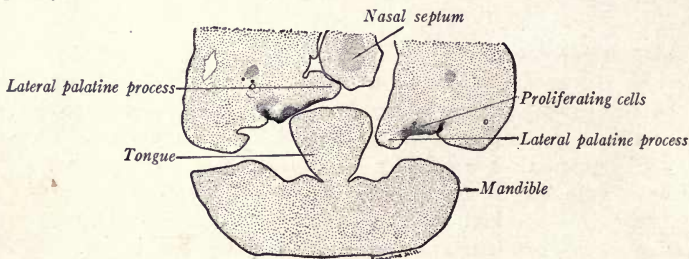


FIG. 154.—Section through the jaws of a 25 mm. pig embryo, to show the change in the position of the palatine processes with reference to the tongue.

After the withdrawal of the tongue, the lateral palatine processes take up a horizontal position and their edges are approximated because the cells on the ventral sides of the folds proliferate more rapidly than those of the dorsal side (Schorr, 1908). That the change in position of the palatine folds is not mechanical, but due to unequal growth, may be seen in Fig. 154, a section through the palatine folds of a pig embryo that shows the right

palatine fold in a horizontal position, although the left fold projects ventral to the dorsum of the tongue. A region of cellular proliferation may be seen on the under side of each process.

Anomalies.—The lateral palatine processes occasionally fail to unite in the middle line, producing a defect known as *cleft palate*. The extent of the defect varies considerably, in some cases involving only the soft palate, while in other cases both soft and hard palates are cleft. It may also be associated with hare lip.

DEVELOPMENT OF THE TONGUE

The development of the tongue may be studied from dissections of pig embryos 6, 9, and 13 mm. long. As the pharynx is bent nearly at right angles, it is necessary to cut away its roof by two pairs of sections passing in different planes. The first plane of section cuts through the eye and first two branchial arches just above the cervical sinus (Fig. 155, I.). From the surface, the razor blade should be directed obliquely dorsad in cutting toward the median line. Cuts in this plane should be made from either side. In the same way make sections on each side in a plane forming an obtuse angle with the first section and passing dorsal to the cervical sinus (II). Now sever the remaining portion of the head from the body by a transverse section in a plane parallel to the first (III). Place the ventral portion of the head in a watch glass of alcohol, and, under the dissecting microscope, remove that part of the preparation cranial to the mandibular arches. Looking down upon the floor of the pharynx, remove any portions of the lateral pharyngeal wall which may still interfere with a clear view of the pharyngeal arches, as seen in Figs. 98 and 156. Permanent mounts of the three stages mentioned above may be made and used for study by the student.

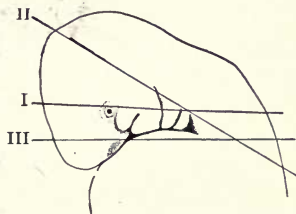


FIG. 155.—Lateral view of the head of a 7 mm. pig embryo. The three lines indicate the planes of sections to be made in dissecting the tongue as described in the text.

The tongue develops as two distinct portions, the *body* and the *root*, separated from each other by a V-shaped groove, the *sulcus terminalis*. In both human and pig embryos the body of the tongue is represented by three anlagen that appear in front of the second branchial arches. These are the median, somewhat triangular *tuberculum impar*, and the paired *lateral swellings* of the first, or mandibular arches, all of which are present in human embryos of 5 mm. (Figs. 98 and 157 A). At this stage, a median ventral elevation formed by the union of the second branchial arches (and, according to some workers, the third as well) constitutes the *copula*. This, with the portions of the second arches lateral to it, forms later the *base*, or *root*, of the tongue. Between it and the *tuberculum impar* is the point of evagination of the *thyroid gland*. The *copula* also connects the *tuberculum impar* with a rounded prominence that is developed in the mid-ventral line from the bases of the third and fourth branchial arches. This is the anlage of the *epiglottis*.

In later stages (Fig. 156 *A* and *B*) the lateral mandibular anlages, bounded laterally by the alveolo-lingual grooves, increase rapidly in size

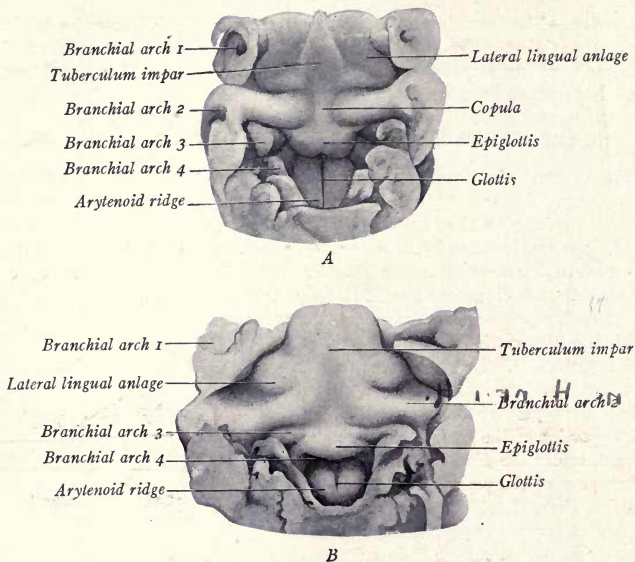


FIG. 156.—Dissections showing the development of the tongue in pig embryos. $\times 12$. *A*, 9 mm. embryo; *B*, 13 mm. embryo.

and fuse with the tuberculum impar, which lags behind in development, and, according to Hammar atrophies completely. The epiglottis becomes

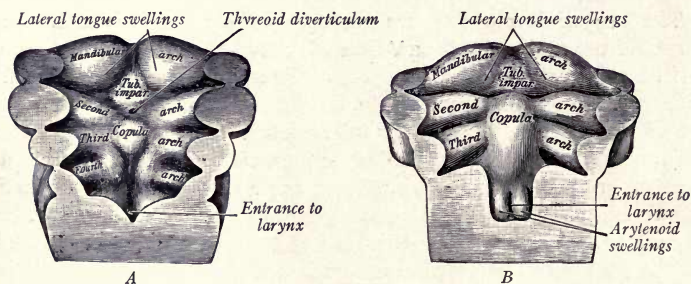


FIG. 157.—The development of the tongue in human embryos. *A*, 5 mm.; *B*, 7 mm. (modified from Peters).

larger and concave on its ventral surface. Caudal to it, and in early stages continuous with it, are two thick rounded folds, the *arytenoid ridges*. Between these is the slit-like *glottis* leading into the *larynx* (see p. 167).

The foregoing account applies to the early origin of the mucous membrane alone. The musculature of the tongue is supplied chiefly by the *hypoglossal nerve*, and both nerve and muscles belong historically to the postbranchial region. If not in the development of each present-day embryo, at least in the past the musculature has migrated cephalad and invaded the branchial region beneath the mucous membrane (cf. p. 320). At the same time, the tongue may be said to extend caudad until its root is covered by the epithelium of the third and fourth branchial arches. This is shown by the fact that the sensory portions of the *nn. trigeminus* and *facialis*, the nerves of the first and second arches, supply the body of the tongue, while the *nn. glossopharyngeus* and *vagus*, the nerves of the third and fourth arches, supply the root and the caudal portion of the body of the tongue.

Anomalies.—Faulty development or incomplete fusion of the several anlagen causes variable degrees of absence or bifurcation of the tongue.

In fetuses of 50 to 60 mm. (CR) the *fungiform* and *filiform papillæ* may be distinguished as elevations of the epithelium. *Taste buds* appear in the fungiform papillæ of 100 mm. (CR) fetuses and are much more numerous in the fetus than in the adult. The *vallate papillæ* (Fig. 158 A) develop on a V-shaped epithelial ridge, the apex of the V corresponding to

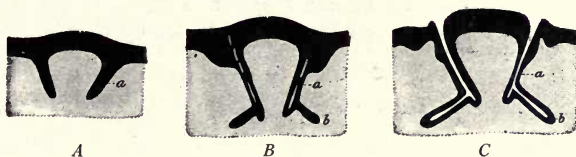


FIG. 158.—Diagrams showing the development of the vallate papillæ of the tongue (Gräberg in McMurrich). *a*, Valley; *b*, von Ebner's gland.

the site of the thyreoid evagination (*foramen cæcum*). At intervals along the epithelial ridges, circular epithelial downgrowths occur (85 mm. CR) which take the form of inverted and hollow truncated cones (Fig. 158). During the fourth month circular clefts appear in the epithelial downgrowths, thus separating the walls of the vallate papillæ from the surrounding epithelium and forming the trench from which this type of papilla derives its name. At the same time, lateral outgrowths arise from the bases of the epithelial cones, hollow out and form the *ducts* and *glands of Ebner*. The taste buds of the vallate papillæ are also formed early, appearing in embryos of three months. *Foliate papillæ* probably develop at about six months.

DEVELOPMENT OF THE SALIVARY GLANDS

The glands of the mouth are all regarded as derivatives of the ectodermal epithelium. They complete their differentiation only after birth.

The *parotid* is the first to appear. Its anlage has been observed in 8 mm. embryos, near the angle of the mouth, as a keel-like flange in the floor of the alveolo-buccal (i.e., jaw-cheek) groove (Hammar). The

flange elongates, and, in embryos of 17 mm., separates from the parent epithelium, forming a tubular structure that opens into the mouth cavity near the front end of the original furrow. The tube grows back into the region of the external ear, branches, and forms the gland in this region, while the stem portion of the tube becomes the parotid duct. Acinus cells are present at five months.

The *submaxillary gland* arises at 11 mm. as an epithelial ridge in the alveolo-lingual (i.e., jaw-tongue) groove, its cephalic end located caudal to the frenulum of the tongue. The caudal end of the ridge soon begins to separate from the epithelium and extends caudad and ventrad into the submaxillary region, where it enlarges and branches to form the gland proper; its cephalic unbranched portion, persisting as the duct, soon hollows out.

The *sublingual gland* develops in 24 mm. embryos as several solid evaginations of epithelium from the alveolo-lingual groove (Fig. 163). This group, usually regarded as a sublingual gland, really consists of the sublingual proper, with its ductus major and of about ten equivalent *alveolo-lingual glands*. Mucin cells have appeared by the sixteenth week.

DEVELOPMENT OF THE TEETH

The teeth have a double origin. The enamel is from ectoderm, the dentine and cement mesodermal.

Enamel Organ.—There first appears in embryos of about 11 mm. an ectodermal downgrowth, the *dental ridge*, or *lamina*, on the future alveolar portions of the upper and lower jaws (Fig. 159). These laminae are parallel and mesial to the labial grooves. At intervals, on each curved dental

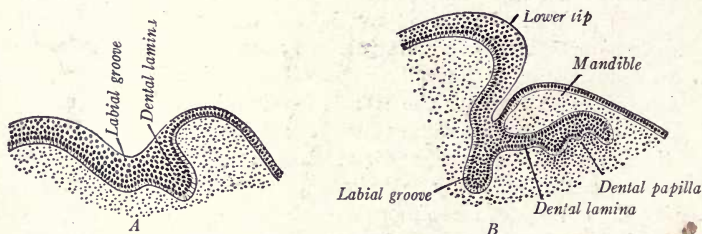


FIG. 159.—Early stages in the development of the teeth (Röse). A, at 17 mm. ($\times 90$); B, at 41 mm. ($\times 45$).

lamina, a series of thickenings develop, the anlagen of the *enamel organs*, which will form enamel and serve as the molds of the future teeth (Fig. 160). Soon, the ventral side of each enamel organ becomes concave (40 mm. C H) forming an inverted cup, and the concavity is occupied by dense mesenchymal tissue, the *dental papilla*, or anlage of the dentine and pulp

(Figs. 159 *B* and 161). An enamel organ with dental papilla forms the anlage of each tooth (Fig. 162). Ten such anlagen of the *deciduous*, or *milk teeth* are present in the upper jaw and ten in the lower jaw of a 40 mm. fetus (Fig. 165). Their connection with the dental ridge is eventually lost.

The internal cells of the enamel organs are at first compact, but later, by the development of an intercellular matrix, the cells separate, forming

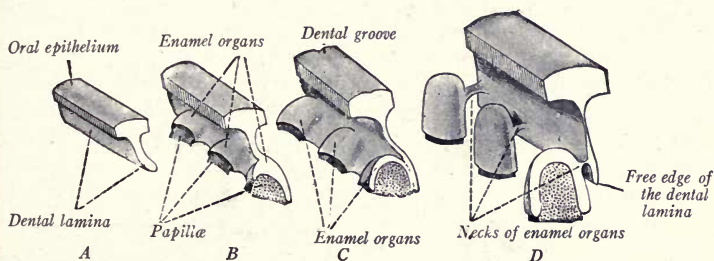


FIG. 160.—Diagrams showing the early development of three teeth, one in section (Lewis and Stöhr).

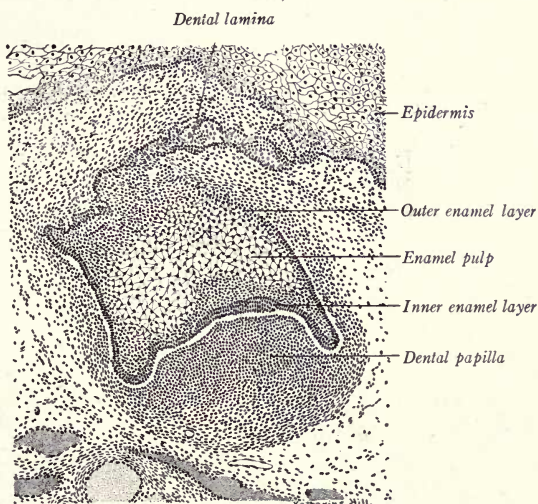


FIG. 161.—Section through an upper incisor from a 65 mm. human fetus. $\times 70$.

a reticulum resembling mesenchyme, termed the *enamel pulp* (Fig. 161). The *outer enamel cells*, at first cuboidal, flatten out and later form a fibrous layer. The *inner enamel cells* bound the cup-shaped concavity of the enamel organ. Over the crown of the tooth, these cells, the *ameloblasts*, become slender and columnar in form, producing the *enamel layer* of the

tooth along their basal ends (Fig. 163). The enamel is laid down first as an uncalcified fibrillar layer which later becomes calcified in the form of enamel prisms, one for each ameloblast. The enamel is formed first at the apex of the crown of the tooth and extends downward toward the root. The enamel cells about the future root of the tooth remain cuboidal or

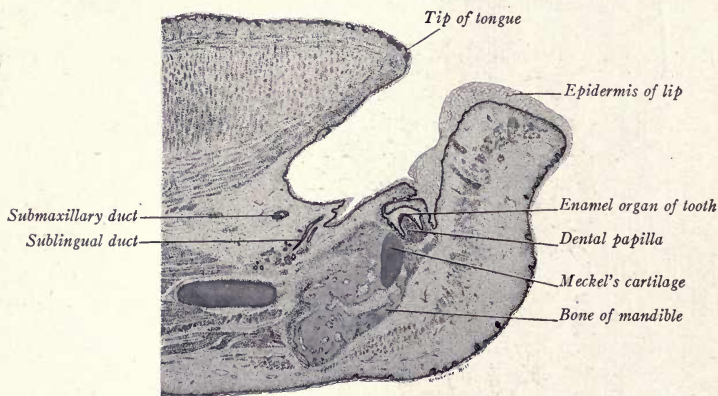


FIG. 162.—Parasagittal section through the mandible and tongue of a 65 mm. human fetus, showing the relations of the first incisor anlage. $\times 14$.

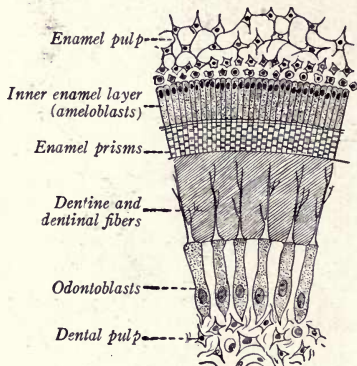


FIG. 163.—Section through a portion of the crown of a developing tooth, showing the various layers (after Tourneux in Heisler).

low columnar in form, come into contact with the outer enamel cells, and the two layers constitute the *epithelial sheath* of the root; it does not produce enamel prisms (Fig. 164).

The Dental Papilla.—The outermost cells of the dental papilla, at the end of the fourth month, arrange themselves as a definite layer of columnar epithelium. Since they produce the *dentine*, or dental bone,

these cells are known as *odontoblasts* (Fig. 164). When the dentine layer is developed, the odontoblast cells remain internal to it, but branched processes from them (the *dentinal fibers* of Tomes) extend into the dentine and occupy the *dental canaliculi* (Fig. 163). Internal to the odontoblast layer, the mesenchymal cells differentiate into the *dental pulp*, popularly

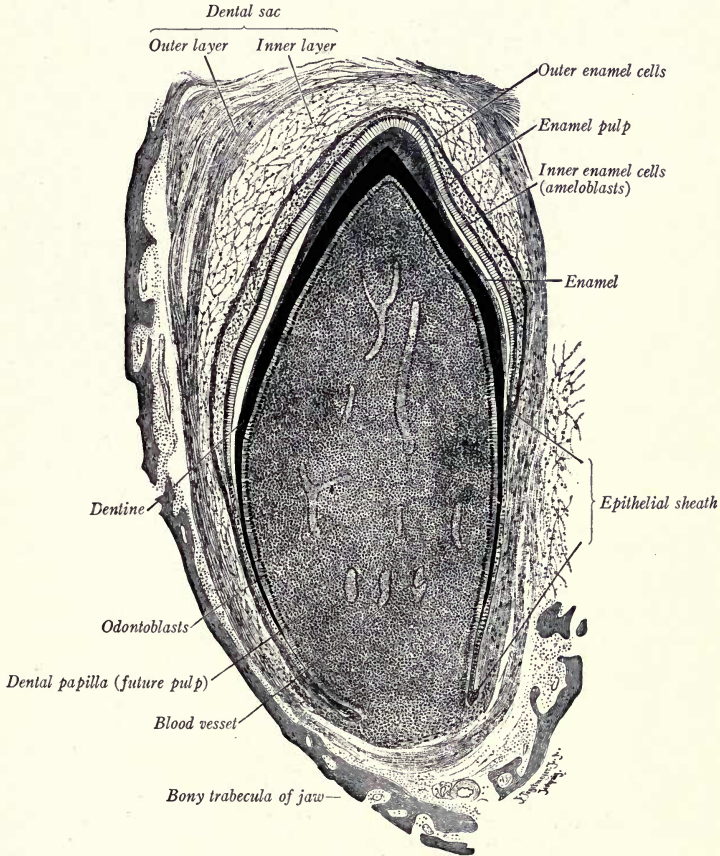


FIG. 164.—Longitudinal section of a deciduous tooth of a newborn dog. $\times 42$. Above the enamel, on either side, are artificial shrinkage spaces. (Lewis and Stöhr).

known as the 'nerve' of the tooth. This is composed of a framework of reticular tissue in which are found blood vessels, lymphatics, and nerve fibers. The odontoblast layer persists throughout life and intermittently lays down dentine, so that eventually the root canal may be obliterated.

The Dental Sac.—The mesenchymal tissue surrounding the anlage of

the tooth gives rise to a dense outer layer and a more open inner layer of fibrous connective tissue. These layers form the *dental sac* (Fig. 164). Over the root of the tooth a layer of *osteoblasts*, or bone forming cells, develops, and, the epithelial sheath formed by the enamel layers having disintegrated, these osteoblasts deposit about the dentine a layer of specialized bone, known as the *cement*. The cement layer contains typical bone cells but no Haversian systems. As the tooth grows and fills the alveolus, the dental sac becomes a thin, vascular layer, the *peridental membrane*. This has fibrous attachments to both the alveolar bone and the cement of the tooth.

When the crown of the tooth is fully developed the enamel organ disintegrates, and, as the roots of the teeth continue to grow, their crowns

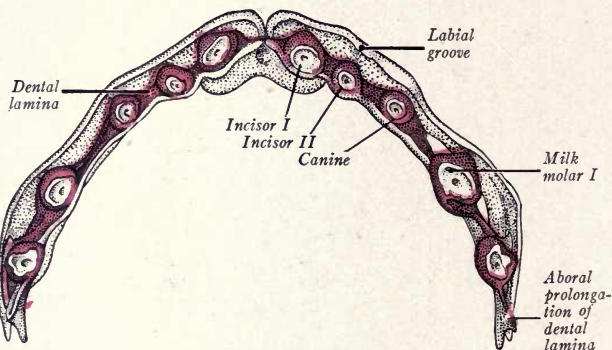


FIG. 165.—Dental lamina and anlagen of the upper milk teeth in a 115 mm. human fetus (Röse).

approach the surface and break through the gums. The periods of eruption of the various *milk*, or *deciduous teeth* vary with race, climate, and nutritive conditions. Usually these teeth are cut in the following sequence:

Median Incisors.....	sixth to eighth month.
Lateral Incisors.....	eighth to twelfth month.
First Molars.....	twelfth to sixteenth month.
Canines.....	seventeenth to twentieth month.
Second Molars.....	twentieth to thirty-sixth month.

The *permanent teeth* develop precisely like the temporary set. The anlagen of those permanent teeth which correspond to the deciduous, or milk teeth, are developed in another series along the free edge of the dental lamina (Fig. 160 D) and come to lie mesad of the deciduous teeth (Fig. 166). In addition, the anlagen of three permanent molars are developed on each side, both above and below, from a backward or aboral extension

of the dental lamina, entirely free from the oral epithelium (Fig. 165.) The anlagen of the first permanent molars appear at seventeen weeks (180 mm. C H), those of the second molars at six weeks after birth, while the anlagen of the third permanent molars, or wisdom teeth, are not found until the fifth year. The permanent dentition of thirty-two teeth is then complete.

Before the permanent teeth begin to erupt, the roots of the milk teeth undergo partial resorption, their dental pulp dies, and they are

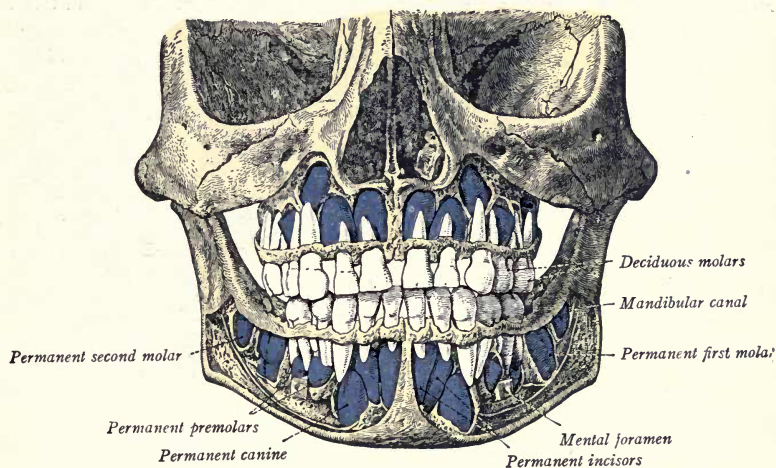


FIG. 166.—Skull of a five-year-old child, showing the positions of the deciduous and permanent teeth (Sobotta-McMurrich).

eventually shed. Toward the sixth year, before the shedding of the deciduous teeth begins, each jaw may contain twenty-six teeth (Fig. 166). The permanent teeth are cut as follows:

First Molars.....	seventh year.
Median Incisors.....	eighth year.
Lateral Incisors.....	ninth year.
First Premolars.....	tenth year.
Second Premolars.....	eleventh year.
Canine	thirteenth to fourteenth year.
Second Molars }	
Third Molars (Wisdom Teeth).....	seventeenth to fortieth year.

The teeth of vertebrates are homologues of the placoid scales of elasmobranch fishes (sharks and skates). The teeth of the shark resemble enlarged scales, and many generations of teeth are produced in the adult fish. In some mammalian embryos three, or even four, dentitions are present. The primitive teeth of mammals are of the canine type, and from this conical tooth the incisors and molars have arisen. Just how the cusped tooth differentiated—whether by the fusion of originally separate units, or by the development of cusps on a single primitive tooth—is debated.

Anomalies.—Dental anomalies are frequent and may consist in the congenital absence of some or all of the teeth, or in the production of more than the normal number. Defective teeth are frequently associated with hare-lip. Cases have been noted in which, owing to defect of the enamel organ, the enamel was entirely wanting. Third dentitions have been recorded, and occasionally fourth molars may be developed behind the wisdom teeth.

CHAPTER VII

THE ENTODERMAL CANAL AND ITS DERIVATIVES: THE BODY CAVITIES

WHEN the head- and tail folds of the embryo develop, there are formed, both cranial and caudal to the spherical vitelline sac, blind entodermal tubes, the *fore-gut* and *hind-gut* respectively (Figs. 79, 255 and 167A). The region between these intestinal tubes, open ventrally into

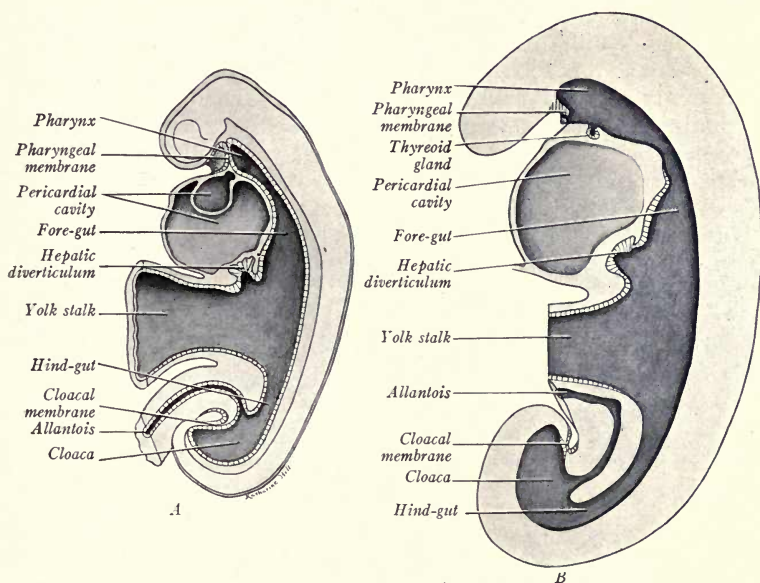


FIG. 167.—Diagrams showing in median sagittal section the human alimentary canal. $\times 35$.
A, 2 mm. embryo (modified after His); B, 2.5 mm. embryo (after Thompson).

the yolk sac, is sometimes termed the *mid-gut*. As the embryo and the yolk sac at first grow more rapidly than the connecting region between them, this region is apparently constricted and becomes the *yolk stalk*, or *vitelline duct*. At either end the entoderm comes into contact ventrally with the ectoderm. Thus there are formed the *pharyngeal membrane* of the foregut and the *cloacal membrane* of the hind-gut. In 2 mm.

embryos the pharyngeal membrane separates the ectoderma mouth cavity, or *stomodæum*, from the pharyngeal cavity of the fore-gut. In front of the membrane is the ectodermal diverticulum, *Rathke's pouch*. In 2.5 to 3 mm. embryos (Fig. 167 B) the pharyngeal membrane ruptures and the stomodæum and pharynx become continuous. The original blind termination of the fore-gut apparently forms *Seessel's pouch*, a temporary landmark of no special significance.

The *fore-gut* later forms part of the oral cavity and is further differentiated into the pharynx and its derivatives, and into the esophagus, respiratory organs, stomach, duodenum, jejunum, and a portion of the ileum. From the duodenum arise the liver and pancreas. The *hind-gut*, beginning at the attachment of the yolk stalk extends caudally to the *cloaca*, into which the *allantois* opens in 2 mm. embryos. The hind-gut is differentiated into the ileum, cæcum, colon, and rectum. The cloaca is subdivided into the *rectum* and *urogenital sinus* (for its development see Chapter VIII). At the same time the cloacal membrane is separated into a urogenital membrane and into an anal membrane. The latter eventually ruptures, forming the *anus*. The yolk stalk usually loses its connection with the entodermal tube in embryos of about 7 mm. (Fig. 179).

We have seen how the palatine processes divide the primitive oral cavity into the nasal passages and mouth cavity of the adult, and have described the development of the tongue, teeth, and salivary glands—organs derived wholly or in part from the ectoderm. It remains to trace the development of the entodermal pharynx and intestinal tract, and their derivatives.

THE PHARYNGEAL POUCHES

There are developed early from the lateral wall of the pharynx paired entodermal outgrowths which are formed in succession cephalo-caudad. In 4 to 5 mm. embryos, five pairs of such *pharyngeal pouches* are present, the fifth pair being rudimentary (Figs. 86 and 87). Meantime, the pharynx has been flattened dorso-ventrally and broadened laterally and cephalad, so that it is triangular in ventral view (Figs. 87 and 168).

From each pharyngeal pouch develop small dorsal and large ventral diverticula. All five pouches come into contact with the ectoderm of corresponding *branchial grooves*, fuse with it, and form the *closing plates*. Although the closing plates become perforate in human embryos only occasionally, these pouches, nevertheless, are homologous to the functional branchial clefts of fishes and tailed amphibia. The first and second pharyngeal pouches soon connect with the pharyngeal cavity through wide common openings. The third and fourth pouches grow laterad and their diverticula communicate with the pharynx through narrow ducts in 10 to

12 mm. embryos (Fig. 168). When the cervical sinus (p. 91) is formed, the ectoderm of the second, third, and fourth branchial clefts is drawn out to produce the transient *branchial* and *cervical ducts* and the *cervical vesicle*. These are fused at the closing plates with the entoderm of the second, third, and fourth pharyngeal pouches.

The fate of these entodermal pouches is varied and spectacular. The *first* differentiates into the *tympanic cavity* of the middle ear and into

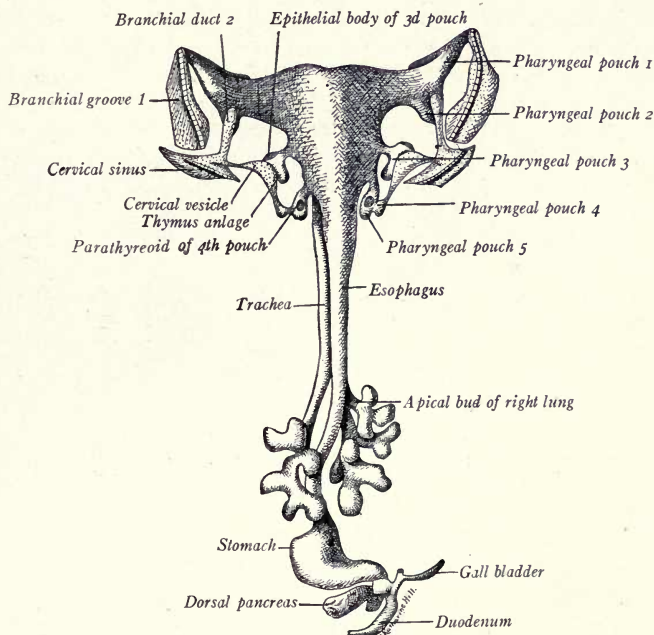


FIG. 168.—A reconstruction of the pharynx and fore-gut of an 11.7 mm. human embryo, seen in dorsal view (after Hammar). The ectodermal structures are stippled.

the *auditory (Eustachian) tube*. The *second* becomes the *palatine tonsil* in part. The *third*, *fourth*, and *fifth* pouches give rise to a series of ductless glands, the *thymus*, *parathyroids*, and the *ultimobranchial bodies*.

THE TONSIL

By the growth and lateral expansion of the pharynx, the second pouch is absorbed into the pharyngeal wall, its dorsal angle alone persisting, to be transformed into the *tonsillar* and *supratonsillar fossæ*. A mound of mesodermal lymphoid tissue presses against the epithelium of the tonsillar fossæ in 140 (CR?) fetuses. This association constitutes the *palatine tonsil*. Crypts arise by the hollowing of solid epithelial ingrowths.

A subepithelial infiltration of lymphocytes during the sixth month gives rise to the median *pharyngeal tonsil*, which like the *lingual tonsil* is not of pharyngeal pouch origin. Immediately caudad is a recess, the *pharyngeal bursa*, formed by a protracted connection of the epithelium with the notochord (Huber). It bears no relation to Seesel's pouch. According to Hammar, the lateral pharyngeal recess of (Rosenmüller) is not a persistent portion of the second pouch, as His asserted.

Anomalies.—Imperfect closure of the branchial clefts (usually the second) leads to the formation of cysts, diverticula, or even fistulæ.

THE THYMUS

The *thymus anlage* appears in 10 mm. embryos as a ventral and medial prolongation of the third pair of pouches (Figs. 168 and 169). The ducts connecting the diverticula with the pharynx soon disappear so that the thymus anlages are set free. At first hollow tubes, they soon lose their cavities and their lower ends enlarge and migrate caudally into the thorax,

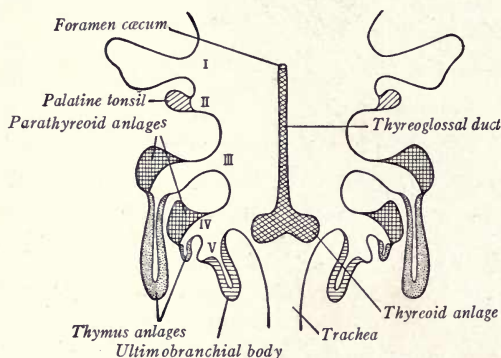


FIG. 169.—Diagram of the pharynx and its derivatives. (Modified after Groschuff and Kohn.)
I-V, first to fifth pharyngeal pouches.

usually passing ventral to the left vena anonyma. Their upper ends become attenuate and atrophy, but may persist as an accessory thymus lobe (Kohn). The enlarged lower ends of the anlages form the body of the gland, which is thus a paired structure (Fig. 170). At 50 mm. (CR) the thymus still contains solid cords and small closed vesicles of entodermal cells. From this stage on, in development, the gland becomes more and more lymphoid in character. Its final position is in the thorax, dorsal to the cranial end of the sternum. It grows under normal conditions until puberty, after which its involution begins. This process proceeds slowly in healthy individuals, rapidly in case of disease. True atrophy of the parenchyma enters at about the fiftieth year.

The *ventral diverticulum* of the fourth pouch is a rudimentary thymic anlage. It usually atrophies.

It is now generally believed that the entodermal epithelium of the thymus is converted into reticular tissue and *thymic corpuscles*. The latter are the atrophic and hyalinized remains of embryonic tubules and cords (Marine, 1915). The lymphoid cells were regarded by Stöhr as entodermal in origin, but most observers derive them from the mesoderm.

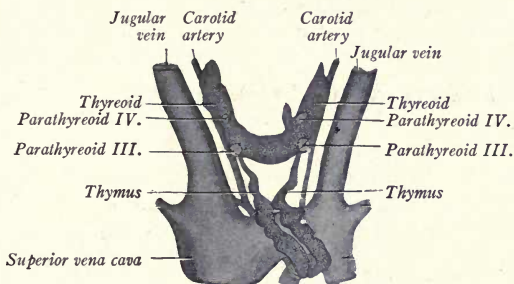


FIG. 170.—Reconstruction of the thymus, thyroid and parathyroid glands in a 26 mm. human embryo (after Tourneaux and Verdun). $\times 15$.

THE PARATHYREOID GLANDS

The *dorsal diverticula* of the third and fourth pharyngeal pouches each give rise to a small mass of epithelial cells termed a *parathyreoid gland* (Fig. 169). Two pairs of these bodies are thus formed, and, with the atrophy of the ducts of the pharyngeal pouches, they are set free and migrate caudalward. They eventually lodge in the dorsal surface of the thyroid gland, the pair from the third pouch lying one on each side at the caudal border of the thyroid in line with the thymus anlagen (Fig. 170). The pair of parathyreoids derived from the fourth pouches are located on each side near the cranial border of the thyroid. Their solid bodies are broken up into masses and cords of polyhedral entodermal cells intermingled with blood vessels. In postfetal life, lumina may appear in the cell masses and fill with a colloid-like secretion.

THE ULTIMOBRANCHIAL OR POSTBRANCHIAL BODIES

The *ultimobranchial body* is the derivative of the fifth pharyngeal pouch (Fig. 169). By the atrophy of the ducts of the fourth pouches they are set free and migrate caudad with the parathyreoids. Each forms a hollow vesicle which has been erroneously termed the *lateral thyroid*. According to Grosser and Verdun, it takes no part in forming thyroid tissue, but atrophies. Kingsbury (1915) denies the origin of the ultimobranchial body from any specific pouch, and asserts it is "merely formed by a continued growth activity in the branchial entoderm."

THE THYROID GLAND

In embryos with five to six primitive segments (1.4 mm). there appears in the mid-ventral wall of the pharynx, between the first and second branchial arches, a small out-pocketing, the *thyroid anlage*. In 2.5 mm. embryos it has become a stalked vesicle (Figs. 167 *B* and 87). Its stalk, the *thyreoglossal duct*, opens at the aboral border of the tuberculum impar of the tongue (Figs. 157 *A*); this spot is represented permanently by the *foramen cæcum* (Fig. 180). The duct soon atrophies and the bilobed gland anlage (Fig. 169) loses its lumen and breaks up into irregular, solid, anastomosing plates of tissue as it migrates caudad. It takes up a transverse position with a lobe on each side of the trachea and larynx (Fig. 170). In embryos of 24 mm., discontinuous lumina begin to appear in swollen portions of the plates; these represent the primitive thyroid follicles (Norris.)

Anomalies—Persistent portion of the thyreoglossal duct may form cysts or even fistulæ.

THE LARYNX, TRACHEA AND LUNGS

In embryos of 23 segments, the anlage of the respiratory organs appears as a groove in the floor of the entodermal tube, just caudal to the

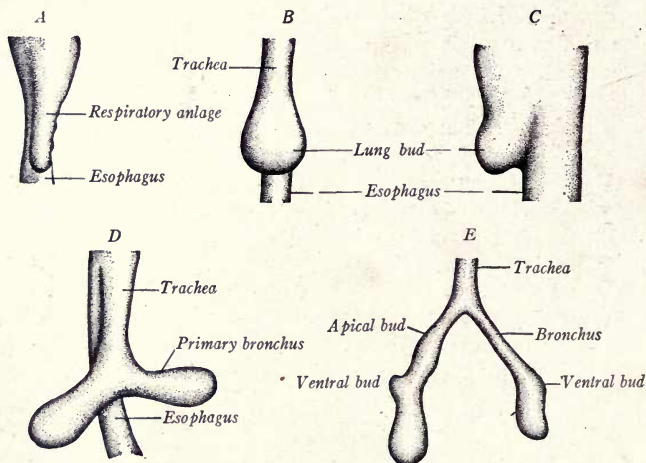


FIG. 171.—Diagrams of stages in the early development of the trachea and lungs of human embryos (based on reconstructions by Bremer, Broman, Grosser, and Narath). \times about 50. *A*, 2.5 mm.; *B*, 4 mm.; *C*, stage *B* in side view; *D*, 5 mm.; *E*, 7 mm.

pharyngeal pouches. This groove produces an external ridge on the ventral wall of the tube, a ridge which becomes larger and rounded at its caudal end (Fig. 171). The *laryngo-tracheal* groove and the ridge are the

anlages of the *larynx* and *trachea*. The rounded end of the ridge is the unpaired anlage of the *lungs*.

Externally, two lateral longitudinal grooves mark off the dorsal esophagus from the ventral respiratory anlages. The lung anlage rapidly increases in size, and becomes bilobed in embryos of 4 to 5 mm. A fusion of the lateral furrows progressing cephalad, constricts first the lung anlages and then the trachea from the esophagus. At the same time the laryngeal portion of the groove and ridge advances cranially until it lies between the fourth branchial arches (Fig. 87). At 5 mm. the respiratory apparatus consists of the laryngeal groove and ridge, the tubular trachea, and the two lung buds (Fig. 711 D).

The Larynx.—In embryos of 5 to 6 mm.

the oral end of the laryngeal groove is bounded on either side by two rounded prominences, the *arytenoid swellings*, which, continuous orally with a transverse ridge, form the *furcula* of His (Fig. 157 B). The transverse ridge becomes the *epiglottis*, and, as we saw in connection with the development of the tongue, it is derived from the third and fourth branchial arches. In embryos of 15 mm. the arytenoid swellings are bent near the middle. Their caudal portions become parallel, while their cephalic portions diverge nearly at right angles (Fig. 172). The *glottis*, opening into the larynx, thus becomes T-shaped and ends blindly, as the laryngeal epithelium has fused. In 40 mm. (CR) fetuses this fusion is dissolved, the arytenoid swellings are withdrawn from contact with the epiglottis, and the entrance to the larynx becomes oval in form (Fig. 173).

At 27 mm. the *ventricles* of the larynx appear, and, at 37 mm. (CR), their margins indicate the position of the *vocal cords*. The elastic and muscle fibers of the cords are developed by the fifth month.

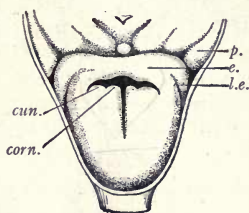


FIG. 172.—Entrance to larynx in a 15 to 16 mm. human embryo (from Kallius). $\times 15$. *p.*, Pharyngo-epiglottic fold; *e.*, epiglottic fold; *l.e.*, lateral part of epiglottis; *cun.*, cuneiform tubercle; *corn.*, corniculate tubercle.

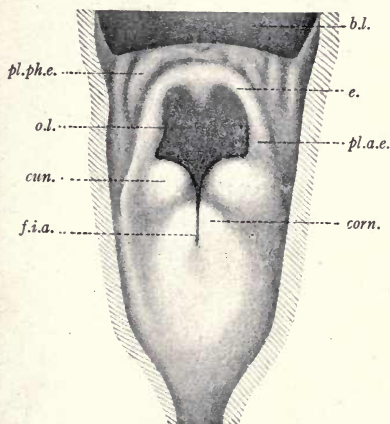


FIG. 173.—The larynx of 160 to 230 mm. human fetus (Soulie and Bardier). $\times 6$. *b.l.*, Base of tongue; *e.*, epiglottis; *f.i.a.*, interarytenoid fissure; *o.l.*, orifice of larynx; *pl.a.e.*, plica ary-epiglottica; *pl.ph.e.*, plica pharyngo-epiglottica; *cun.*, cuneiform tubercle; *corn.*, corniculate tubercle.

At the end of the sixth week the cartilaginous skeleton of the larynx is indicated by surrounding condensations of mesenchyme. The cartilage of the *epiglottis* appears relatively late. The *thyroid cartilage* is formed as two lateral plates, each of which has two centers of chondrification. These plates grow ventrad and fuse in the median plane.

The anlagen of the *cricoid* and *arytenoid cartilages* are at first continuous. Later, separate cartilage centers develop for the arytenoids. The cricoid is at first incomplete dorsad, but eventually forms a complete ring. The cricoid may therefore be regarded as a modified tracheal ring. The *corniculate cartilages* represent separated portions of the arytenoids. The *cuneiform cartilages* are derived from the cartilage of the epiglottis.

The Trachea.—This gradually elongates during development and its columnar epithelium becomes ciliated. Muscle fibers and the anlagen of the cartilaginous rings appear at 17 mm. The glands develop as ingrowths of the epithelium during the last five months of fetal life.

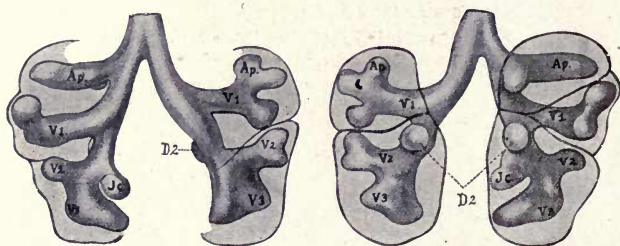


FIG. 174.—Ventral and dorsal views of the lungs from a human embryo of about 9 mm. (after Merkel). Ap., Apical bronchus; D1, D2, etc., dorsal, V1, V2, ventral bronchi; Jc. infracardiac bronchus.

The Lungs.—Soon after the lung anlagen, or *stem buds*, are formed (in 5 mm. embryos), the right bronchial bud becomes larger and is directed more caudally (Fig. 171). At 7 mm. the stem bronchi give rise to two bronchial buds on the right side, to one on the left. The smaller bronchial bud on the right side is the *apical bud*. The right and left chief buds, known as *ventral bronchi*, soon bifurcate. There are thus formed three bronchial rami on the right side two on the left, and these correspond to the primitive lobes of the lungs (Figs. 168 and 174).

On the left side, an apical bud is interpreted as being derived from the first ventral bronchus (Fig. 174). It develops later and remains small so that a lobe corresponding to the upper lobe of the right lung is not developed (Narath). The upper lobe of the left lung thus would correspond to the upper and middle lobes of the right lung.

The bronchial anlagen continue to branch in such a way that the stem bud is retained as the main bronchial stem (Fig. 174). That is, the branching is monopodial, not dichotomous, lateral buds being given off from the stem bud proximal to its growing tip. Only in the later stages of develop-

ment has dichotomous branching of the bronchi and the formation of two equal buds been described. Such buds, formed dichotomously, do not remain of equal size (Flint).

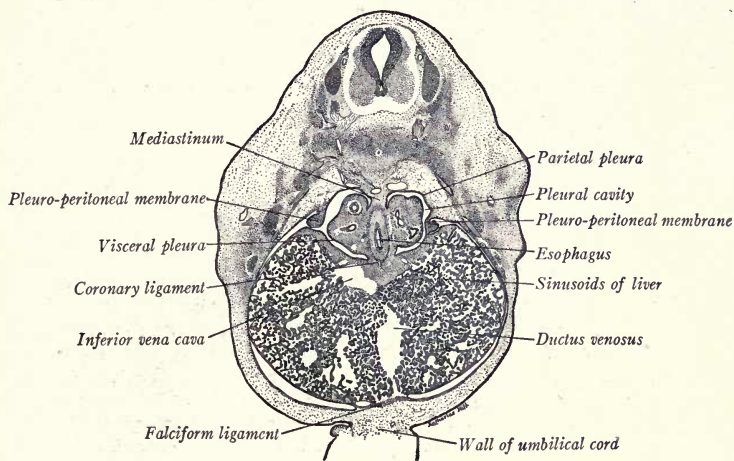


FIG. 175.—Transverse section through the lungs and pleural cavities of a 10 mm. human embryo. $\times 23$.

The entodermal anlagen of the lungs and trachea are developed in a median mass of mesenchyme dorsal and cranial to the peritoneal cavity. This tissue forms a broad mesentery termed the *mediastinum* (Fig. 175). The right and left stem buds of the lungs grow out laterad, carrying with them folds of the mesoderm. The branching of the bronchial buds takes place within this tissue which is covered by the mesothelial lining of the body cavity. The terminal branches of the bronchi are lined with entodermal cells; these flatten out and form the *respiratory epithelium* of the adult lungs. The surrounding mesenchyme differentiates into the muscle, connective tissue, and cartilage plates of the lung, tracheal, and bronchial walls. Into it grow blood vessels and nerve fibers. When the pleural cavities are separated from the pericardial and peritoneal cavities, the mesothelium covering

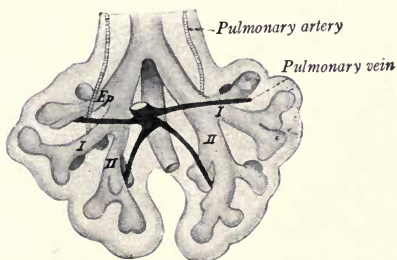


FIG. 176.—Ventral view of the lungs of a 10.5 mm. embryo, showing the pulmonary arteries and veins (His in McMurrich). $\times 27$. *Ep.*, Apical bronchus; *I*, *II*, primary bronchi.

the lungs, with the connective tissue underlying it, becomes the *visceral pleura*. The corresponding layers lining the thoracic wall form the *parietal pleura*. These layers are derived respectively from the visceral (splanchnic) and parietal (somatic) mesoderm of the embryo.

In 11 mm. embryos the two *pulmonary arteries*, from the sixth pair of aortic arches, course lateral then dorsal to the stem bronchi (Fig. 176). The right pulmonary artery passes ventral to the apical bronchus of the right lung. The single *pulmonary vein* receives two branches from each lung, a larger vein from each lower lobe, a smaller vein from each upper lobe, including the middle lobe of the right side. These four pulmonary branches course ventrad and drain into the pulmonary trunk. When this common stem is taken up into the wall of the left atrium, the four pulmonary veins open directly into the latter.

According to Kölliker, the air cells, or *alveoli*, of the lungs begin to form in the sixth month and their development is completed during pregnancy. Elastic tissue appears during the fourth month in the largest bronchi. The abundant connective tissue found between the bronchial branches in early fetal life becomes reduced in its relative amount as the alveoli of the lungs are developed.

Before birth the lungs are small, compact, and possess sharp margins. They lie in the dorsal portion of the pleural cavities. After birth they normally fill with air, expanding and completely filling the pleural cavities. Their margins become rounded and the compact fetal lung tissue, which resembles that of a gland in structure, become light and spongy, owing to the enormous increase in the size of the alveoli and blood vessels. Because of the greater amount of blood admitted to the lungs after birth, their weight is suddenly increased.

Anomalies.—Variations occur in the size and number of lobes of the lungs; rarely there is a third lobe on the left side. In the most common anomaly involving both esophagus and trachea, the esophagus is divided transversely, the trachea opening into the lower segment, while the upper portion ends as a blind sac.

THE ESOPHAGUS, STOMACH AND INTESTINE

The Esophagus.—The esophagus in 4 to 5 mm. embryos* is a short tube, flattened laterally, extending from the pharynx to the stomach. It grows rapidly in length, and in 7.5 mm. embryos its diameter decreases both relatively and absolutely (Forssner). At this stage the esophageal *epithelium* is composed of two layers of columnar cells, but at birth they number nine or ten.

In 20 mm. embryos, vacuoles appear in the epithelium and increase the size of the lumen, which, however, is at no time occluded. Glands begin to develop as epithelial ingrowths at 78 mm. (CR). The circular muscle layer is indicated at 10 mm. but the longitudinal muscle fibers do not form a definite layer until 55 mm. (C R). These layers appear in similar time-sequence throughout the entire digestive tract.

Anomalies.—There may be atresia. This usually involves fistulous relations with the trachea, as already described (p. 170).

The Stomach.—The stomach appears in embryos of 4 to 5 mm. as a laterally flattened, fusiform enlargement of the fore-gut caudal to the lung anlagen (Figs. 177 and 178). Its epithelium is early thicker than that of esophagus and is surrounded by a heavy layer of *splanchnic mesoderm*. It is attached dorsally to the body wall by its mesentery, the *greater omentum*, and ventrally to the liver by the *lesser omentum* (Fig. 190 B). The dorsal border of the stomach both bulges locally to form the *fundus*, and also grows more rapidly than the ventral wall throughout its extent, thus producing the convex *greater curvature*. The whole stomach becomes curved and its cranial end is displaced to the left by the enlarging

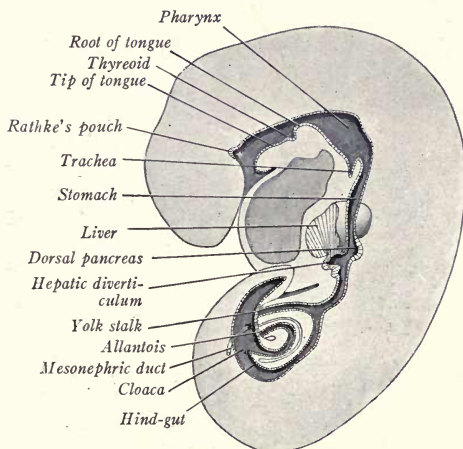


FIG. 177.—Median sagittal section of a 5 mm. human embryo, to show the digestive canal (modified after Ingalls). $\times 14$.

liver (Fig. 168). This forms a ventral concavity, the *lesser curvature*, and produces the first flexure of the duodenum.

The rapid growth of the gastric wall along its greater curvature also causes the stomach to rotate upon its long axis until its greater curvature, or primitive dorsal wall, lies to the left, its ventral wall, the lesser curvature, to the right (Fig. 201). The original right side is now dorsal, the left side ventral in position, and the caudal, or pyloric end of the stomach is ventral and to the right of its cardiac, or cephalic end. The whole organ extends obliquely across the peritoneal cavity from left to right (cf. Fig. 138). The change in position progresses rapidly and is already completed early in the second month (12 to 15 mm.). The rotation of the stomach explains the asymmetrical position of the vagus nerves of the adult organ,

the left nerve supplying the ventral wall of the stomach, originally the left wall, while the right vagus supplies the dorsal wall, originally the right.

In 17 mm. embryos the stomach has reached its permanent position, the cardiac having descended through about ten segments, the pylorus through six or seven.

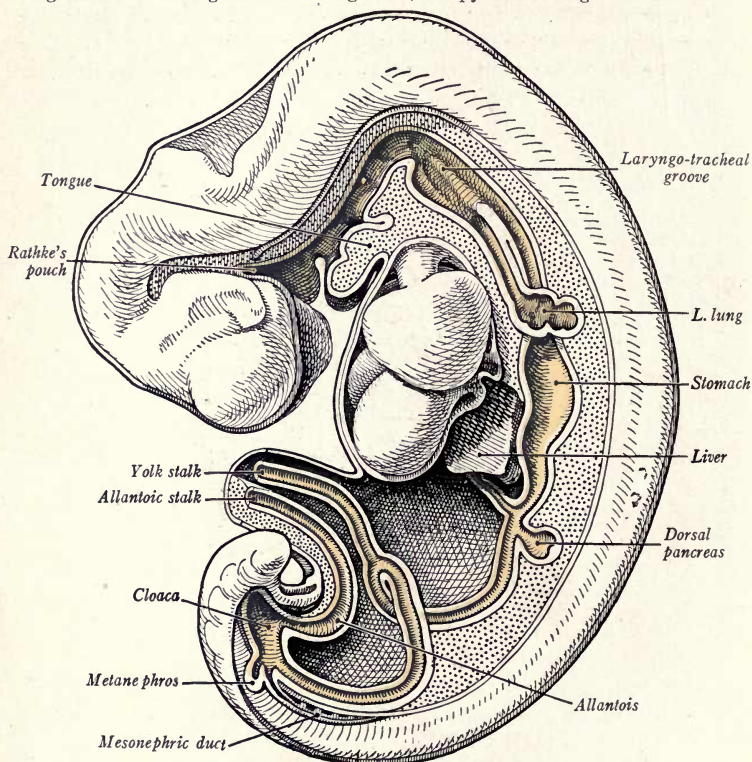


FIG. 178.—Reconstruction of a 5 mm. human embryo, showing the entodermal canal and its derivatives (His in Kollmann). $\times 25$.

Gastric pits are indicated in 16 mm. embryos, and, at 100 mm. (C R), glands cells of the *gastric glands* are differentiated from the gastric epithelium. The gastric pits number 270,000 at birth but increase by fission to nearly 7 million in the adult. The *cardiac glands* are developed early (91 mm. (C R) fetuses).

At 10 mm. the stomach wall is composed of three layers: the *entodermal epithelium*, a thick *mesenchymal* layer, and the peritoneal *mesothelium*. At 16 mm. the circular muscle layer is indicated by condensed mesenchyma; a heavier ring forms the *pyloric sphincter*. At 91 mm. (C R) the cardiac region shows a few longitudinal muscle fibers, which become distinct in the pyloric region at 240 mm. (CR).

The Intestine.—In 5 mm. embryos (Fig. 177), the intestine, beginning at the stomach, consists of the *duodenum* (from which are given off the hepatic diverticulum and dorsal pancreas), and the *cephalic* and *caudal limbs of the intestinal loop*, which bends ventrad and connects with the *yolk stalk*. Caudally, the intestinal tube expands to form the *cloaca*. It is supported from the dorsal body wall by the *mesentery* (Fig. 178).

From 5 to 9 mm. the ventral bend of the intestinal loop becomes more marked and the attachment of the yolk stalk to it normally disappears

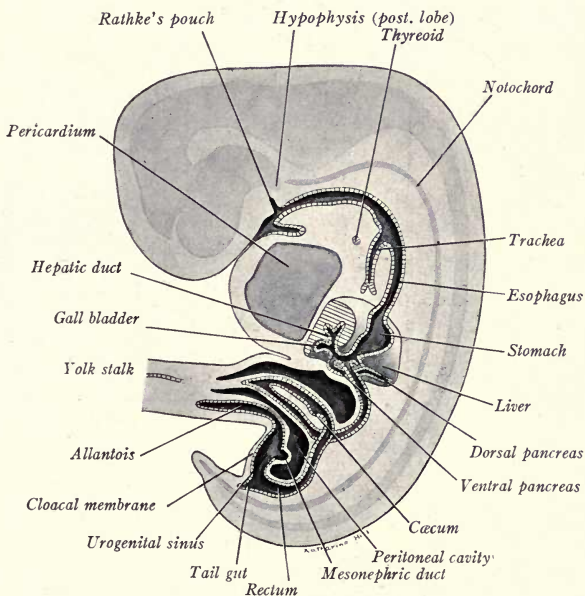


FIG. 179.—Diagram, in median sagittal section, showing the digestive canal of a 9 mm. human embryo (adapted from Mall). $\times 9$.

(Fig. 179). At this stage the dorsal pancreatic anlage has been developed from the duodenum, and, in the caudal limb of the intestinal loop, there is formed an enlargement, due to a ventral bulging of the gut wall, that marks the anlage of the *cæcum* and the boundary line between the *large* and *small intestine*.

Succeeding changes in the intestine consist: (1) in its torsion and coiling, due to its rapid elongation, and (2) in the differentiation of its several regions. As the gut elongates in 9 to 10 mm. embryos, the intes-

tinal loop rotates. As a result, its caudal limb lies at the left and cranial to its cephalic limb (Fig. 179).

The *small intestine* soon lengthens rapidly, and, at 17 mm. (Fig. 180), forms loops within the umbilical cord. This constitutes a normal umbilical hernia. Six primary loops occur and these may be recognized in the arrangement of the adult intestine. In embryos of 42 mm. the intestine has returned from the umbilical cord into the abdominal cavity through a rather small aperture; the coelom of the cord is soon after obliterated.

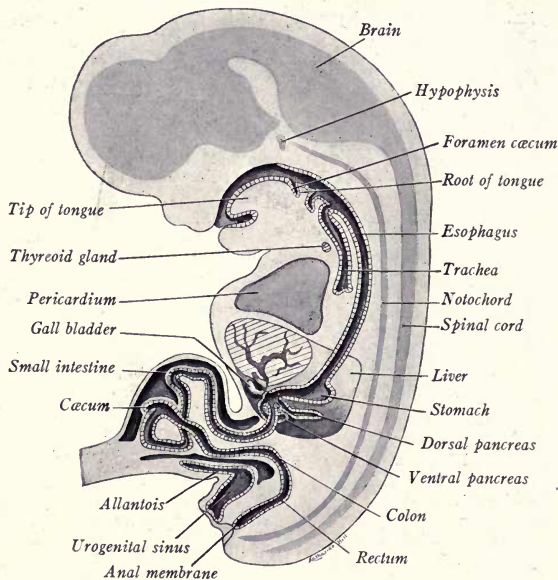


FIG. 180.—Diagrammatic median sagittal section of a 17 mm. human embryo, showing the digestive canal (modified after Mall). $\times 5$.

In embryos between 10 and 30 mm., vacuoles appear in the wall of the duodenum and epithelial septa completely block the lumen. The remainder of the small intestine remains open, although vacuoles form in its epithelium. *Villi* appear as rounded elevations of the epithelium at 23 mm. (Johnson). They begin to form at the cephalic end of the jejunum, and, at 130 mm. (CR), they are found throughout the small intestine (Berry). *Intestinal glands* appear as ingrowths of the epithelium about the bases of the villi. They develop first in the duodenum at 91 mm. (CR). The *duodenum glands* (of Brunner) are said to appear during the fourth month (Brand). In embryos of 10 to 12.5 mm. the circular muscle layer of the intestine first forms. The longitudinal muscle layer is not distinct until 75 mm. (CR).

The *large intestine*, as seen in 9 mm. embryos (Fig. 179), forms a tube extending from the cæcum to the cloaca. It does not lengthen so rapidly

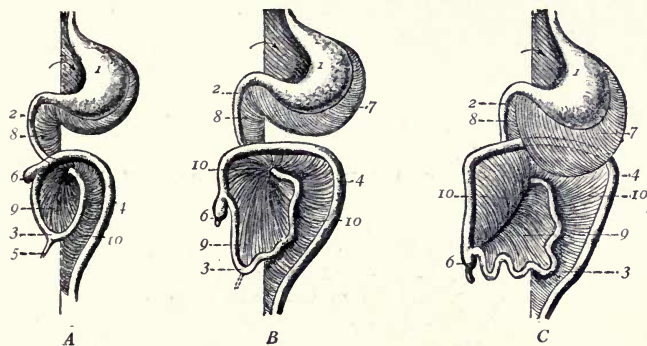


FIG. 181.—Three stages showing the development of the digestive tube and the mesenteries in the human fetus (Tourneux in Heisler). 1, Stomach; 2, duodenum; 3, small intestine; 4, colon; 5, yolk stalk; 6, cæcum; 7, great omentum; 8, mesoduodenum; 9, mesentery, 10, mesocolon. The arrow points to the orifice of the omental bursa. The ventral mesentery is not shown.

as the small intestine, and, when the intestine is withdrawn from the umbilical cord (at 42 mm. C R), its cranial, or cæcal end lies on the right side

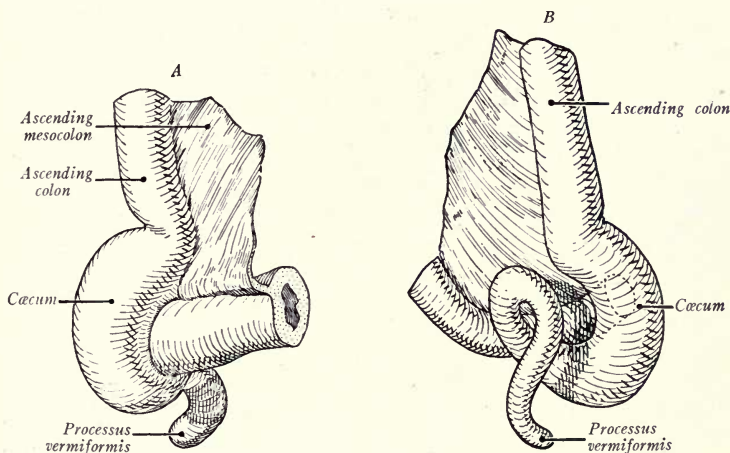


FIG. 182.—The cæcum and vermiform process of a human fetus of 50 mm. (Kollmann): A, from the ventral side; B, from the dorsal side.

and dorsal to the small intestine (Fig. 181). It extends transversely to the left side as the *transverse colon*, then, bending abruptly caudad as the

descending colon, returns by its *iliac flexure* to the median plane and forms the *rectum*. In stages between 100 and 200 mm. (CR) the lengthening of the colon causes the cæcum and cephalic end of the colon to descend toward the pelvis (Fig. 181). The *ascending colon* thus takes the position which it occupies in the adult.

The distal end of the cæcal anlage early lags in development, and, at 65 mm. (CR), the *vermiform process* is distinct from the *cæcum*. These structures make a sharp U-shaped bend with the colon at 42 mm. (CR), and this flexure gives rise to the *colic valve* (Toldt).

The circular muscle layer of the large intestine appears first at 23 mm., the longitudinal layer at 75 mm. (C R). In 55 mm. (C R) fetuses villi are present.

Glandular secretions and desquamated entodermal cells, together with swallowed amniotic fluid, containing lanugo hairs and vernix caseosa, collect in the fetal intestine. This mass, yellow to brown in color, is known as *meconium*. At birth the intestine and its contents are perfectly sterile.

Anomalies.—The intestine may show atresia. This occurs most often in the duodenum as a retention of the embryonic occlusion (p. 174).

In 2 per cent of all adults there is a persistence of the proximal end of the yolk stalk to form a pouch, Meckel's *diverticulum of the ileum*. This varies between 3 and 9, or more, cm. in length and lies about 80 cm. above the colic valve. It is clinically important as it may cause intestinal strangulation in infants.

Congenital *umbilical hernia* is due either to the continuance of the normally transitory embryonic condition or to a secondary protrusion of the viscera. Other hernias are explained on pp. 195 and 225.

THE LIVER

In embryos of 2.5 mm. the liver anlage is present as a median ventral outgrowth from the entoderm of the fore-gut, just cranial to the yolk stalk (Fig. 167 B). Its thick walls enclose a cavity which is continuous with that of the gut.

This *hepatic diverticulum* becomes embedded at once in a mass of splanchnic mesoderm, the *septum transversum*. Cranially, the septum will contribute later to the formation of the diaphragm; caudally, in the region of the liver anlage, it becomes the ventral mesentery (Fig. 189). Thus, from the first, the liver is in close relation to the septum trans-

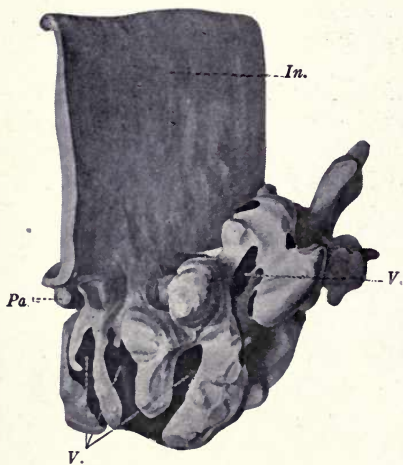


FIG. 183.—Model of the liver anlage of a 4 mm. human embryo (Bremer). $\times 160$. In., Intestine; Pa., pancreas; V., veins in contact with liver trabeculae.

versum, and later when the septum becomes a part of the diaphragm the liver remains attached to it.

In embryos 4 to 5 mm. long, solid cords of cells proliferate from the ventral and cranial portion of the hepatic diverticulum (Fig. 86). These cords anastomose and form a crescentic mass with wings extending dorsal and lateral to the gut (Fig. 177). This mass, a network of solid trabeculae, is the glandular portion of the liver. The primitive, hollow diverticulum later differentiates into the gall bladder and the large biliary ducts.

Referring to Fig. 88, it will be seen that the liver anlage lies between the vitelline veins and is in close proximity to them laterally. The veins send anastomosing branches into the ventral mesentery. The trabeculae of the expanding liver grow between and about these venous plexuses, and



FIG. 184.—The trabeculae and sinusoids of the liver in section (after Minot). $\times 300$. *Tr.*, Trabeculae of liver cells; *Si.*, sinusoids.

the plexuses in turn make their way between and around the liver cords (Fig. 183). The vitelline veins on their way to the heart are thus surrounded by the liver and largely subdivided into a network of vessels termed *sinusoids*. The endothelium of the sinusoids is closely applied to the cords of liver cells, which, in the early stages, contain no bile capillaries (Fig. 184). The transformation of the vitelline veins into the portal vein and the relations of the umbilical veins to the liver will be treated in Chapter IX.

The glandular portion of the liver grows rapidly, and, in embryos of 7 to 8 mm., is connected with the primitive hepatic diverticulum by a single cord of cells only, the *hepatic duct* (Fig. 185 A). That portion of the hepatic diverticulum distal to the hepatic duct is now differentiated into the terminal, solid *gall bladder* and its *cystic duct*. Its proximal portion forms the *ductus choledochus*. In embryos of 10 mm. (Fig. 185 B), the

gall bladder and ducts have become longer and more slender. The hepatic duct receives a right and left branch from the corresponding lobes of the liver. The gall bladder is without a lumen up to the 15 mm. stage. Later its cavity appears, surrounded by a wall of high, columnar epithelium.

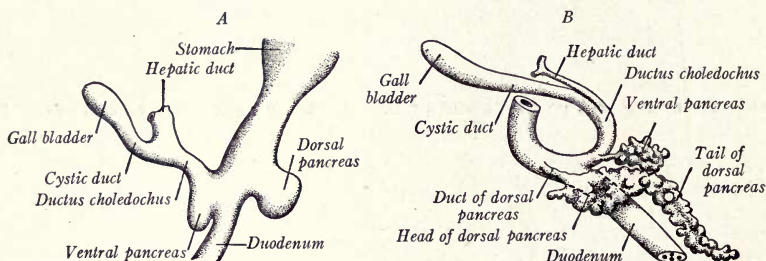


FIG. 185.—Reconstructions showing the development of the hepatic diverticulum and pancreatic anlagen. A, 7.5 mm. human embryo (after Thyng), $\times 50$; B, 10 mm. human embryo, $\times 33$.

The glandular portion of the liver develops fast and is largest relative to the size of the body at 31 mm. (Jackson). In certain regions the liver tissue undergoes degeneration, and especially is this true in the peripheral

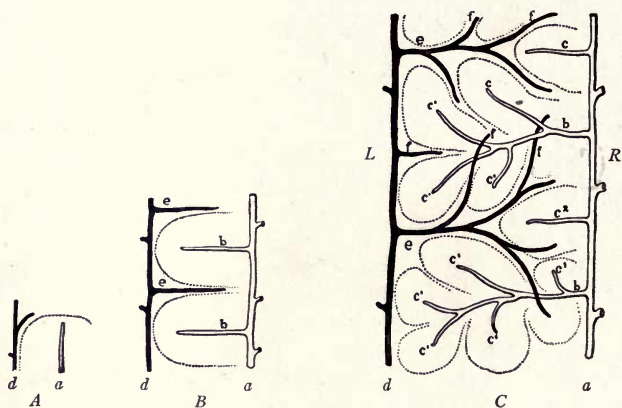


FIG. 186.—Diagrams of three stages of the portal and hepatic veins in a growing liver: a, Hepatic side; d, portal side; b and c, successive stages of the hepatic vein; e and f, successive stages of the portal vein (Mall).

portion of the left lobe. In general, the external lobes of the liver are moulded under the influence of the fetal vitelline and umbilical trunks.

The development of the ligaments of the liver is described on p. 193.

During the development of the liver the endothelial cells of the sinusoids become stellate in outline, and thus form an incomplete layer. From the second month of fetal life to some time after birth, blood cells are actively developed between the hepatic cells and the endothelium of the sinusoids. At 22 mm. hollow *interlobular ducts* develop, spreading inward from the hepatic duct along the larger branches of the portal vein. In 44 mm. (C R) fetuses, *bile capillaries* with cuticular borders are present, most numerous near the interlobular ducts with which some of them connect. At birth, or shortly after, the number of liver cells surrounding a bile capillary is reduced to two, three, or four. Secretion of the bile commences at about the end of the third fetal month.

The lobules, or vascular units of the liver, are formed, according to Mall, by the peculiar and regular manner in which the veins of the liver branch. The primary branches of the portal vein extend along the periphery of each primitive lobule, parallel to similar branches of the hepatic veins that drain the blood from the center of each lobule (Fig. 186). As development proceeds, each primary branch becomes a stem, giving off on either side secondary branches which bear the same relation to each other and to new lobules as did the primary branches to the first lobule. This process is repeated until thousands of liver lobules are developed.

Until the 20 mm. stage, the *portal vein* alone supplies the liver. The *hepatic artery*, from the coeliac axis, comes into relation first with the hepatic duct and gall bladder. Later, it grows into the connective tissue about the larger bile ducts and branches of the portal vein, and also supplies the capsule of the liver.

Anomalies.—A common anomaly of the liver consists in its subdivision into multiple lobes. Absence or duplication of the gall bladder and of the ducts may occur. In some animals (horse, elephant) the gall bladder is normally absent.

THE PANCREAS

Two pancreatic anlagen are developed almost simultaneously in embryos of 3 to 4 mm. The *dorsal pancreas* arises as a hollow outpocketing of the dorsal duodenal wall, just cranial to the hepatic diverticulum (Fig. 177). At 7.5 mm. it is separated from the duodenum by a slight constriction and extends into the dorsal mesentery (Fig. 185 A). The *ventral pancreas* develops in the inferior angle between the hepatic diverticulum and the gut (Lewis), and its wall is at first continuous with both. With the elongation of the ductus choledochus its origin is transferred to this portion of the diverticulum.

Of the two pancreatic anlagen, the dorsal grows more rapidly, and, in 10 mm. embryos, forms an elongated structure with a central duct and irregular nodules upon its surface (Fig. 185 B). The ventral pancreas is smaller and develops a short, slender duct that opens into the ductus choledochus. When the stomach and duodenum rotate, the pancreatic ducts shift their positions as well. At the same time, growth and bending of the bile duct to the right bring the ventral pancreas into close proximity with the dorsal pancreas (Figs. 185 and 187).

In embryos of 20 mm., the tubules of the dorsal and ventral pancreatic anlagen interlock (Fig. 187 B). Eventually, anastomosis takes place be-

tween the two ducts, and the duct of the ventral pancreas, plus the distal segment of the dorsal duct, persists as the functional *pancreatic duct* (of Wirsung) of the adult. The proximal portion of the dorsal pancreatic duct forms the *accessory duct* (of Santorini), which remains pervious, but becomes a tributary of the chief pancreatic duct. The ventral pancreas forms part of the head and uncinete process of the adult gland. The dorsal pancreas takes part in forming the head and uncinete process, and comprises the whole of the body and tail.

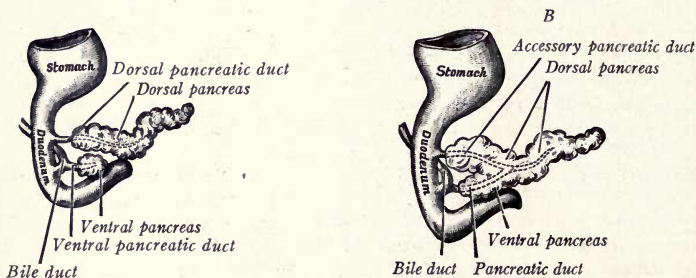


FIG. 187.—Two stages showing the development of the human pancreas: A, Embryo of 8 mm.; B, embryo of about 20 mm. (after Kollmann).

In 10 mm. embryos the portal vein separates the two pancreatic anlagen, and later they partially surround the vein. The *alveoli* of the gland are developed from the ducts as darkly staining cellular buds in fetuses of 40 to 55 mm. (C R). The *islands* characteristic of the pancreas also bud from the ducts (and alveoli, Mironescu, 1910) and appear first in the tail at 55 mm. (C R).

Owing to the shift in the position of the stomach and duodenum during development, the pancreas takes up a transverse position, its tail extending to the left. To its ventral surface is attached the transverse mesocolon.

Anomalies.—The ventral pancreas may arise directly from the intestinal wall, and paired ventral anlagen also occur. Accessory pancreases are not uncommon. Both the dorsal and ventral ducts persist in the horse and dog; in the sheep and man the ventral duct becomes of chief importance; in the pig and ox the dorsal duct.

THE BODY CAVITIES, DIAPHRAGM AND MESENTERIES

The Primitive Cœlom and Mesenteries.—In the Peters embryo the primary mesoderm has already split to form the extra-embryonic cœlom (Fig. 74 C). When the intra-embryonic mesoderm differentiates, numerous clefts appear on either side between the somatic and splanchnic layers of mesoderm. These clefts coalesce in the cardiac region and form two elongated *pericardial cavities*, lateral to the paired, tubular heart. Similarly, right and left *pleuro-peritoneal cavities* are formed between the mesoderm layers caudal to the heart. The paired pericardial cavities

extend toward the midplane cranial to the heart and communicate with each other (Fig. 188). Laterally they are not continuous with the extra-embryonic cœlom, for the head of the embryo separates early from the underlying blastoderm. The pericardial cavities also are prolonged caudally until they open into the pleuro-peritoneal cavities. These in turn communicate laterally with the extra-embryonic cœlom. In an embryo of 2 mm. the cœlom thus consists of a U-shaped pericardial cavity, the right and left limbs of which are continued caudally into the paired pleuro-peritoneal cavities; these extend out into the extra-embryonic cœlom.

When the head fold and fore-gut of the embryo are developed, the layers of splanchnic mesoderm containing the heart tubes are folded together ventral to the fore-gut and form the *ventral mesentery* between the gut and the ventral body wall (Fig. 190). Owing to the position of the yolk, sac, the caudal extent of the ventral mesentery is limited. On each side, at the level where the vitello-umbilical trunk (Fig. 88) courses to the heart, the splanchnic mesoderm and the somatic mesoderm are united (cf. Fig. 110). Thus is

formed the *septum transversum*, which incompletely partitions the cœlom into a cranial and caudal portion (Fig. 189). Cranial to the septum, the heart is suspended in the ventral mesentery which forms the *dorsal* and *ventral mesocardia* (Fig. 190 A). Into the ventral mesentery, caudal to the septum, grows the liver. This portion of the ventral mesentery gives rise dorsally to the *lesser omentum* of the stomach, and, where it fails to separate from the septum transversum, it forms the ligaments of the liver. Ventrally it persists as the *falciform ligament* (Fig. 190 B).

Dorsal to the gut, the splanchnic mesoderm of each side is folded together in the median sagittal plane to constitute the *dorsal mesentery* which extends to the caudal end of the digestive canal (Figs. 189 and 190 C). This suspends the stomach and intestine from the dorsal body wall and is divided into the *dorsal mesogastrum*, or *greater omentum* of the stomach, the *mesoduodenum*, the *mesentery proper* of the small intestine, the *mesocolon*, and the *mesorectum*.

The covering layers of the viscera, mesenteries, and body wall are continuous with each other and consist of a mesothelium overlying con-

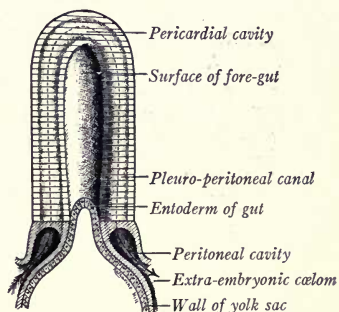


FIG. 188.—Diagrammatic model of the fore-gut and cœlom in an early human embryo, viewed from above and behind (modified after Robinson).

nective tissue. The parietal lining is derived from the somatic layer of mesoderm and the visceral covering from the splanchnic layer.

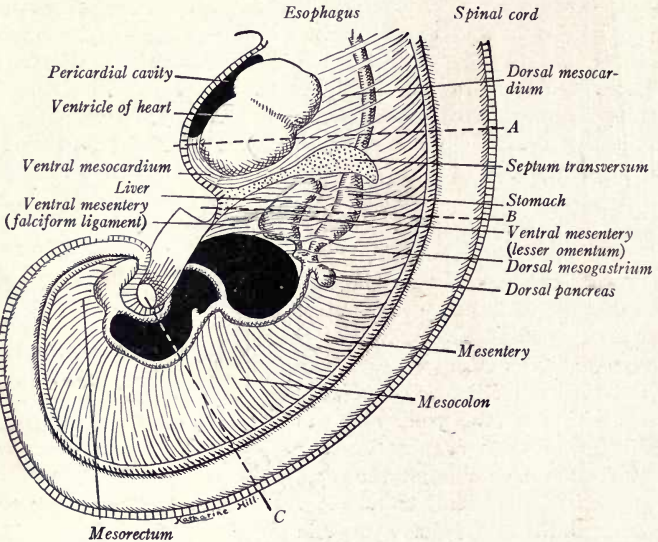


FIG. 189.—Diagram showing the primitive mesenteries of an early human embryo in median sagittal section. The broken lines (A, B, and C) indicate the level of sections A, B, and C, in Fig. 190.

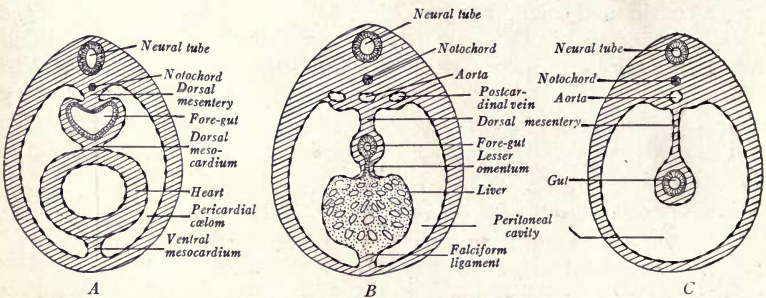


FIG. 190.—Diagrammatic transverse sections of an early human embryo. A, Through the heart and pericardial cavities; B, through the fore-gut and liver; C, through the intestine and peritoneal cavity.

The *primitive cœlom* lies in the horizontal plane, as in Fig. 188. Coincident with the caudal regression of the septum transversum, the pericardial cavity is bent ventrad and enlarged (Fig. 191). The ventral

mesocardium, attaching the heart to the ventral body wall, disappears and the right and left limbs of the U-shaped cavity become confluent, ventral to the heart. The result is a single, large pericardial chamber, the long axis of which now lies in a dorso-ventral plane nearly at right angles to the plane of the pleuro-peritoneal cavities, and connected with them dorsally by the right and left pleuro-peritoneal canals.

The division of the primitive coelom into separate cavities is accomplished by the development of three membranes that join in a Y-shaped fashion (Figs. 194 and 195): (1) the *septum transversum*, which separates

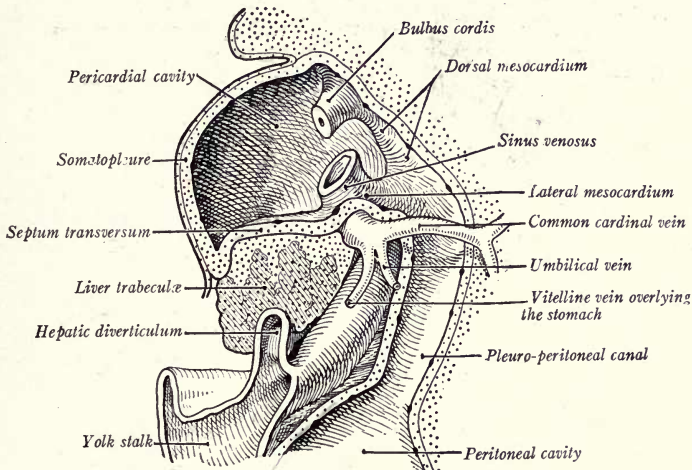


FIG. 191.—Reconstruction cut at the left of the median sagittal plane of a 3 mm. human embryo, showing the body cavities and septum transversum (Kollmann).

incompletely the pericardial and pleural cavities from the peritoneal cavities; (2) the paired *pleuro-pericardial membranes*, which complete the division between pericardial and pleural cavities; (3) the paired *pleuro-peritoneal membranes*, which complete the partition between each pleural cavity, containing the lung, and the peritoneal cavity, which contains the abdominal viscera.

The Septum Transversum.—The vitelline veins, on their way to the heart, course in the splanchnic mesoderm lateral to the fore-gut. In embryos of 2 to 3 mm. these large vessels bulge into the coelom until they meet and fuse with the somatic mesoderm (Figs. 88 and 110). Thus there is formed caudal to the heart a transverse partition filling the space between the sinus venosus of the heart, the gut, and the ventral body wall, and separating the pericardial and peritoneal cavities from each other

ventral to the gut. This mesodermal partition was termed by His the *septum transversum*. In Fig. 191 it comprises both a cranial portion (designated "septum transversum"), that is the anlage of a large part of the diaphragm, and a caudal portion, the ventral mesentery, into which the liver is growing.

At first the septum transversum does not extend dorsal to the gut, but leaves on either side a *pleuro-peritoneal canal* through which the pericardial and pleuro-peritoneal cavities communicate (Fig. 191). In embryos of 4 to 5 mm. the lungs develop in the median walls of these canals and bulge laterally into them. Thus the canals become the *pleural cavities* and will be so termed hereafter.

On account of the more rapid growth of the embryo, there is an apparent constriction at the yolk stalk, and, with the development of the umbilical cord, the peritoneal cavity is finally separated from the extra-embryonic coelom. Dorsally, the pleural and peritoneal cavities are permanently partitioned lengthwise by the dorsal mesentery.

The *septum transversum* in 2 mm. embryos occupies a transverse position in the middle cervical region (Fig. 192, 2). According to Mall, it migrates caudally, its ventral position at first moving more rapidly so that its position becomes oblique. In 5 mm. embryos (Fig. 192, 5) it is opposite the fifth cervical segment, at which level it receives the phrenic nerve. In stages

later than 7 mm., the septum migrates caudad, until, at 24 mm., it is opposite the first lumbar segment. During this second period of migration its dorsal attachment travels faster than its ventral portion. Therefore, it rotates to a position nearly at right angles to its plane in 7 mm. embryos, and its original dorsal surface becomes its ventral surface.

The Pleuro-pericardial and Pleuro-peritoneal Membranes.—The common cardinal veins (ducts of Cuvier), on their way to the heart, curve around the pleural cavities laterally in the somatic body wall (Figs. 191

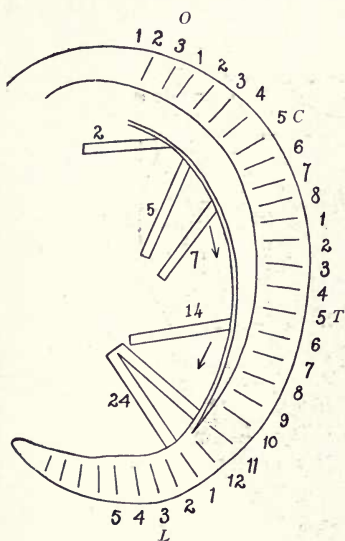


FIG. 192.—Diagram showing the change in position of the septum transversum (modified after Mall). Numerals indicate the length of the embryo at each position of the septum. The letters and numbers at the right represent the segments of the occipital, cervical, thoracic and lumbar regions.

and 193). In embryos of 7 mm., each vein, with the overlying mesoderm, forms a ridge that projects from the body wall mesially into the pleural canals. This ridge, the *pulmonary ridge* (of Mall), is the anlage of both the pleuro-pericardial and pleuro-peritoneal membranes. Later it broadens and thickens cranio-caudally (Fig. 193), forming a triangular structure whose apex is continuous with the septum transversum (Fig. 194). Its cranial side forms the *pleuro-pericardial membrane*, and, in 9 to 10 mm.

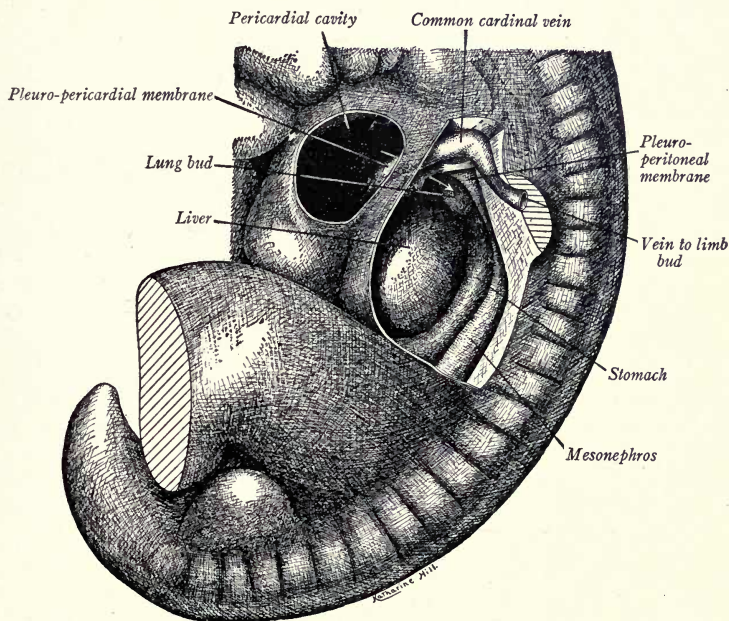


FIG. 193.—Reconstruction of a 7 mm. human embryo, showing from the left side the pleuro-pericardial membrane, the pleuro-peritoneal membrane and the septum transversum (after Mall). $\times 20$. The phrenic nerve courses in the pleuro-pericardial membrane. An arrow passes from pericardial to peritoneal cavity through the pleuro-pericardial canal.

embryos, reduces the opening between the pleural and pericardial cavities to a mere slit. Its caudal side becomes the *pleuro-peritoneal membrane*, which eventually separates dorsally the pleural from the peritoneal cavity (Fig. 195). The two sets of membranes at first lie nearly in the sagittal plane and a portion of the lung is caudal to the pleuro-peritoneal membranes (Fig. 193). Between the stages of 7 and 11 mm. the dorsal attachment of the septum transversum is carried caudally more rapidly

than its ventral portion, and its primary ventral surface becomes its dorsal side (Figs. 192 to 194). The pleuro-peritoneal membrane is carried caudad with the septum transversum until the lung lies in the angle between the pleuro-peritoneal and pleuro-pericardial membranes and is included within the spherical triangle which has been described above (Fig. 194). During this rotation the dorsal end of the *pleuro-pericardial membrane* lags behind and so takes up a position in a coronal plane nearly at right angles to the septum transversum (Figs. 194 and 195). In 11 mm.

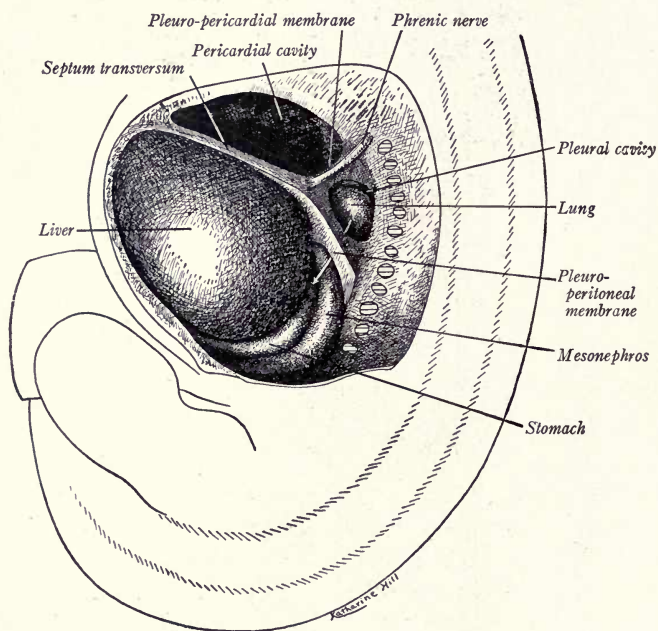


FIG. 194.—Reconstruction of an 11 mm. human embryo, to show the same structures as in Fig. 193 at a later stage (after Mall). $\times 14$.

embryos the pleuro-pericardial membranes have fused completely on each side with the median walls of the pleural canals and thus separate the pericardium from the paired pleural cavities. By way of the pleuro-pericardial membranes the phrenic nerves course to the septum transversum (Fig. 194).

The *pleuro-peritoneal membranes* are continuous dorsally and caudally with the mesonephric folds; ventrally and caudally they fuse later with the *dorsal pillars of the diaphragm*, or *coronary appendages* of the liver

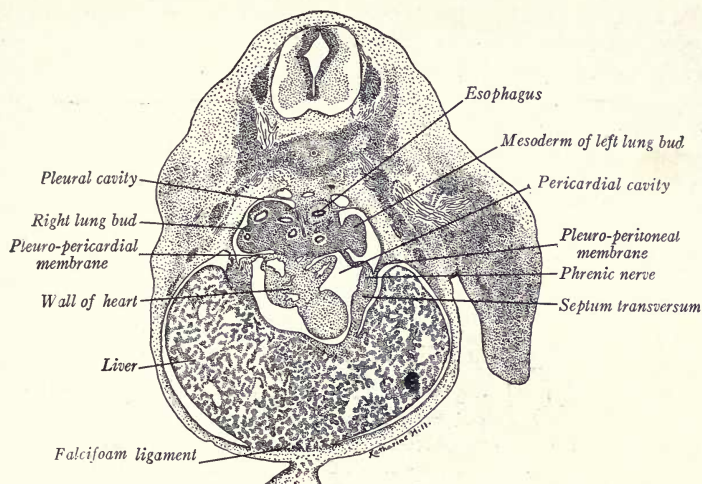


FIG. 195.—Transverse section through a 10 mm. human embryo, showing the pleuro-pericardial membranes separating the pericardium from the pleural cavities. $\times 33$.

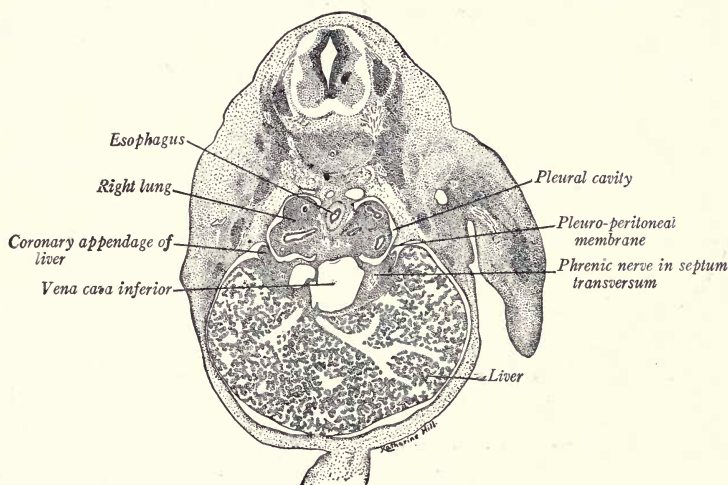


FIG. 196.—Transverse section through a 10 mm. human embryo, showing the pleuro-peritoneal membranes. $\times 16$.

(Lewis) (Fig. 196). Between the free margins of the membranes and the mesentery a temporary opening is left on each side, through which the pleural and peritoneal cavities communicate (Figs. 175, 194 and 200).

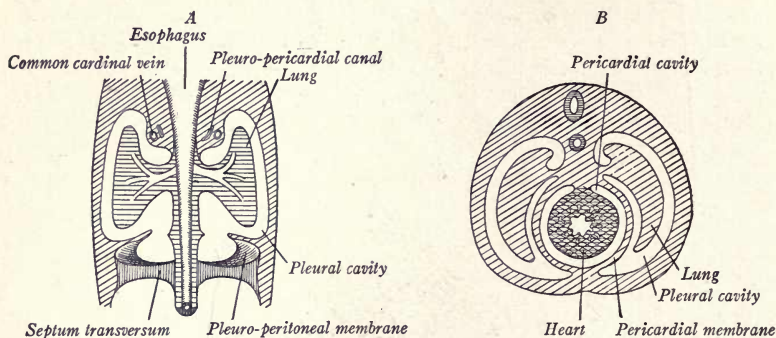


FIG. 197.—Diagrams showing the development of the lungs and the formation of the pericardial membrane (modified after Robinson). A, Coronal section; B, transverse section.

Owing to the caudal migration of the septum transversum and the growth of the lungs and liver, the pleuro-peritoneal membrane, at first lying in a nearly sagittal plane (Fig. 193), is shifted to a horizontal position (Fig. 194), and gradually its free margin unites with the dorsal pillars of the diaphragm and with the dorsal mesentery. The opening between the pleural and peritoneal cavities is thus narrowed and finally closed in embryos of 19 to 20 mm.

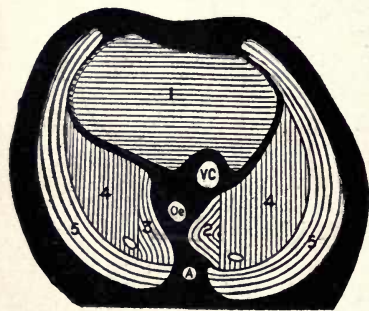


FIG. 198.—Diagram showing the origin of the diaphragm (after Broman). 1, Septum transversum; 2, 3, derivatives of mesentery; 4, 4, derivatives of pleuro-peritoneal membrane; 5, 5, parts derived from the body wall; A, aorta; Oe, esophagus; VC, inferior vena cava.

As the lungs burrow laterally and ventrally into the body wall around the pericardial cavity, the pleuro-pericardial membranes enlarge at the expense of this tissue and more and more the heart comes to lie in a mesial position between the lungs (Fig. 197 B). The pleural cavities thus increase rapidly in size.

The Diaphragm and Pericardial Membrane.—The lungs grow and expand not only cranially and caudally but also laterally and ventrally (Fig. 197). Room is made for them by the obliteration of the very loose, spongy mesenchyme of the adjacent body wall (Fig. 196). As the lungs burrow laterally and ventrally into the body wall around the pericardial cavity, the pleuro-pericardial membranes enlarge at the expense of this tissue and more and more the heart comes to lie in a mesial position between the lungs (Fig. 197 B). The pleural cavities thus increase rapidly in size.

At the same time the liver grows enormously, and on either side a portion of the body wall is taken up into the septum transversum and pleuro-peritoneal membranes. The *diaphragm*, according to Broman, is thus derived from four sources (Fig. 198): (1) its ventral pericardial portion from the septum transversum; its lateral portions from (2) the pleuro-peritoneal membranes, plus (3) derivatives from the body wall; lastly, a median dorsal portion is formed from (4) the dorsal mesentery. In addition to these, the striated muscle of the diaphragm, according to Bardeen (1900), takes its origin from a pair of premuscle masses which in 9 mm. embryos lie one on each side opposite the fifth cervical segment.

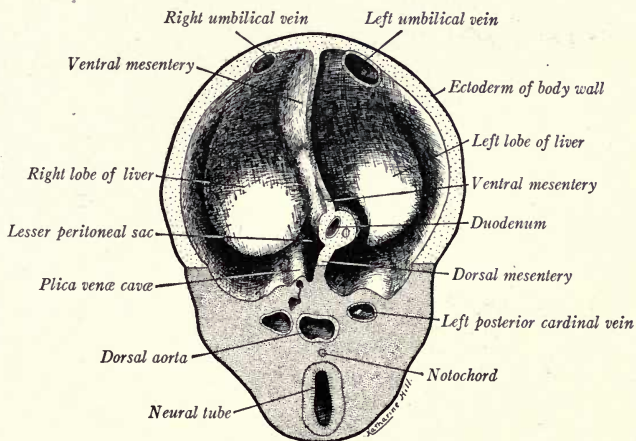


FIG. 199.—Diagrammatic model of an embryo of 7 to 9 mm., showing the position of the lesser peritoneal sac. The embryo is represented as sectioned transversely, caudal to the liver, so that one looks at the caudal surface of the section and of the liver, and cranially into the body cavities.

This is the level at which the phrenic nerve enters the septum transversum. The exact origin of these muscle masses is in doubt, but they probably represent portions of the cervical myotomes of this region. The muscle masses migrate caudally with the septum transversum and develop chiefly in the dorsal portion of the diaphragm (Bardeen, 1900).

The cavities of the mesodermal segments are regarded as portions of the coelom, but in man they disappear early. The development of the vaginal sacs which grow out from the inguinal region of the peritoneal cavity into the scrotum will be described in Chapter VIII.

The Omental Bursa or Lesser Peritoneal Sac.—According to Broman, the *omental bursa* is represented in 3 mm. embryos by a peritoneal pocket which extends cranially into the dorsal mesentery, to the right of the esophagus. A similar pocket present on the left side has disappeared in 4 mm. embryos. Lateral to the opening of the primitive lesser peritoneal sac, a lip-like fold of the mesentery is continued caudally along the dorsal

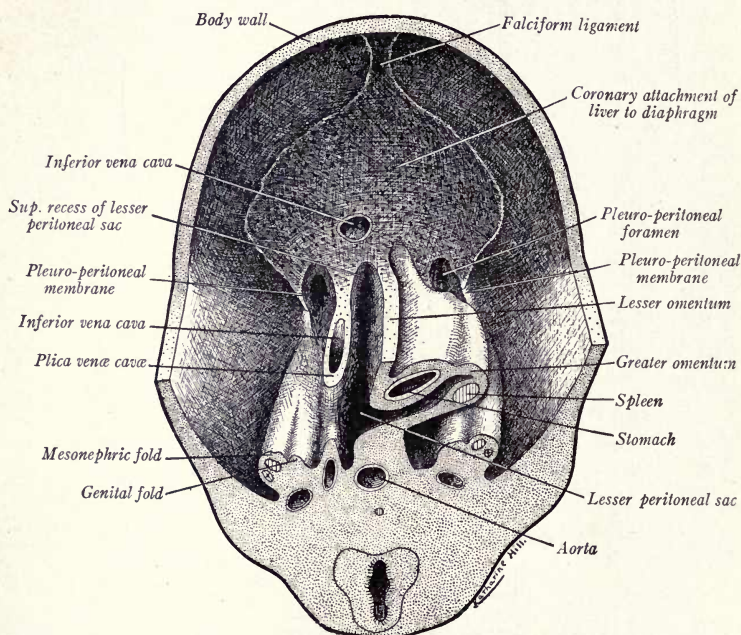


FIG. 200.—A diagrammatic ventral view of the middle third of a human embryo, 12 to 15 mm. long. The figure shows the caudal surface of a section through the stomach and spleen, a ventral view of the stomach, the liver having been cut away to leave the sectioned edges of the lesser omentum and plica venæ cavæ, and the caudal surface of the septum transversum and pleuro-peritoneal membrane. Upon the surface of the septum is indicated diagrammatically the attachment of the liver. (Based on figures of Mall and F. T. Lewis and model by H. C. Tracy.)

body wall into the mesonephric fold as the *plica venæ cavæ*, in which the *inferior vena cava* later develops (Fig. 199). The liver, it will be remembered, grows out into the ventral mesentery from the fore-gut, and, expanding laterally and ventrally, takes the form of a crescent. Its right lobe comes into relation with the plica venæ cavæ, and, growing rapidly caudad, forms with the plica a partition between the lesser sac and the

peritoneal cavity. Thus the cavity of the lesser peritoneal sac is extended caudally from a point opposite the bifurcation of the lungs to the level of the pyloric end of the stomach. In 5 to 10 mm. embryos it is crescent-shaped in cross section (cf. Fig. 111) and is bounded mesially by the greater omentum (dorsal mesentery) and the right wall of the stomach, laterally by the liver and plica venæ cavæ, and ventrally by the lesser omentum (ventral mesentery). It communicates to the right

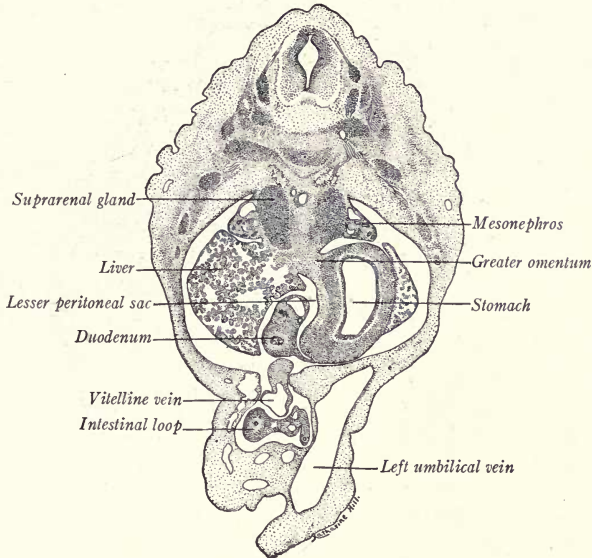


FIG. 201.—An obliquely transverse section through a 10 mm. human embryo at the level of the epiploic foramen (of Winslow). $\times 33$.

with the peritoneal cavity through an opening between the liver ventrally and the plica venæ cavæ dorsally (Figs. 181 and 201). This opening is the *epiploic foramen* (of Winslow). When the dorsal wall of the stomach rotates to the left, the greater omentum is carried with it to the left of its dorsal attachment. Its tissue grows actively to the left and caudally and gives the omentum an appearance of being folded on itself between the stomach and the dorsal body wall (Fig. 200). The cavity of the lesser peritoneal sac is carried out between the folds of the greater omentum as the *inferior recess* of the omental bursa.

From the cranial end of the sac there is constricted off a small closed cavity which is frequently persistent in the adult. This is the *bursa infracardiaca* and may be regarded as a third pleural cavity. It lies at the right of the esophagus in the mediastinum.

When the stomach changes its position and form so that its mid-ventral line becomes the lesser curvature and lies to the right, the position of the lesser omentum is also shifted. From its primitive location in a median sagittal plane, with its free edge directed caudally, it is rotated through 90° until it lies in a coronal plane with its free margin facing to the right (Fig. 201). The epiploic foramen now forms a slit-like opening leading from the peritoneal cavity into the vestibule of the omental bursa. The foramen is bounded ventrally by the edge of the lesser omentum, dorsally by the inferior vena cava, cranially by the caudate process of the liver, and caudally by the wall of the duodenum.

During fetal life the greater omentum grows rapidly to the left and caudad, in the form of a sac, flattened dorso-ventrally. It overlies the

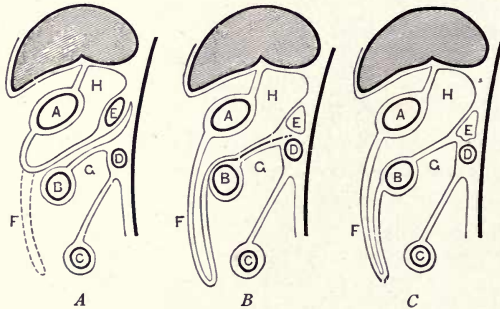


FIG. 202.—Diagrams showing the development of the mesenteries (Hertwig). *A* illustrates the beginning of the great omentum and its independence of the transverse mesocolon; in *B* the two come into contact; in *C* they have fused. *A*, stomach; *B*, transverse colon; *C*, small intestine; *D*, duodenum; *E*, pancreas; *F*, greater omentum; *G*, greater sac; *H*, omental bursa.

intestines ventrally and contains the inferior recess of the omental bursa (Fig. 202). The dorsal wall of the sac during the fourth month usually fuses with the transverse colon where it overlies the latter (Fig. 202 *B*). Caudal to this attachment the walls of the greater omentum may be fused and its cavity is then obliterated. The inferior recess of the omental bursa thus may be limited in the adult chiefly to a space between the stomach and the dorsal fold of the greater omentum, which latter is largely fused to the peritoneum of the dorsal body wall. The *spleen* develops in the cranial portion of the greater omentum and that portion of the omentum which extends between the stomach and spleen is known as the *gastro-licnic ligament* (Fig. 200). The dorsal wall of the omentum between the spleen and kidney is the *lienorenal ligament*.

Further Differentiation of the Mesenteries.—*Ligaments of the Liver.*—

We have seen (p. 181) that the cranial portion of the ventral mesentery forms the mesocardium of the heart. In the ventral mesentery, caudal to the septum transversum, the liver develops. From the first, it is enveloped in folds of the splanchnic mesoderm; as the liver increases in size, these give rise to its *capsule* and *ligaments* (Fig. 190 B). Wherever the liver is unattached, the mesodermal layers of the ventral mesentery form its capsule (of Glisson), a fibrous layer covered by mesothelium, continuous with that of the peritoneum (Fig. 190 B). Along its mid-dorsal and mid-ventral line the liver remains attached to the ventral mesentery. The dorsal attachment between the liver, stomach, and duodenum is the *lesser omentum*. This in the adult is differentiated into the *duodeno-hepatic* and *gastro-hepatic ligaments*. The attachment of the liver to the ventral body wall extends caudally to the umbilicus and forms the *falciform ligament*.

In its early development the liver abuts upon the septum transversum, and, in 4 to 5 mm. embryos, is attached to it along its cephalic and ventral surfaces. Soon, dorsal prolongations of the lateral liver lobes, the *coronary appendages*, come into relation with the septum dorsally and laterally. The attachment of the liver to the septum transversum now has the form of a crescent, the dorsal horns of which are the coronary appendages (Fig. 200). This attachment becomes the *coronary ligament* of the adult liver. The dorso-ventral extent of the coronary ligament is reduced during development and its lateral extensions upon the diaphragm give rise to the *triangular ligaments* of each side.

The right lobe of the liver, as we have seen, comes into relation along its dorsal surface with the *plica venæ cavæ* in 9 mm. embryos (Figs. 199 and 200). This attachment extends the coronary ligament caudally on the right side and makes possible the connection between the veins of the liver and mesonephros which contributes to the formation of the inferior vena cava. The portion of the liver included between the plica venæ cavæ and the lesser omentum is the *caudate lobe* (of Spigelius).

In a fetus of five months the triangular ligaments mark the position of the former lateral coronary appendages. The umbilical vein courses in a deep groove along the ventral surface of the liver, and, with the portal vein and gall bladder, bounds the *quadrate lobe*.

Changes in the Dorsal Mesentery.—That part of the digestive canal which lies within the peritoneal cavity is suspended by the *dorsal mesentery*, which at first forms a simple attachment extending in the median sagittal plane between body wall and primitive gut. That portion of it connected with the stomach forms the *greater omentum*, the differentiation of which has been described (p. 192). The mesentery of the intestine is carried

out into the umbilical cord between the limbs of the intestinal loop. When the intestine elongates and its loop rotates, the cæcal end of the large intestine comes to lie cranially and to the left, the small intestine caudally and to the right, the future duodenum and colon crossing in close proximity to each other (Fig. 179). On the return of the intestinal loop into the abdomen from the umbilical cord, the cæcal end of the colon lies to the right and the transverse colon crosses the duodenum ventrally and cranially (Fig. 203 A). The primary loops of the small intestine lie caudal and to the left of the ascending colon (Fig. 203 B). There has thus been a torsion of the mesentery about the origin of the superior

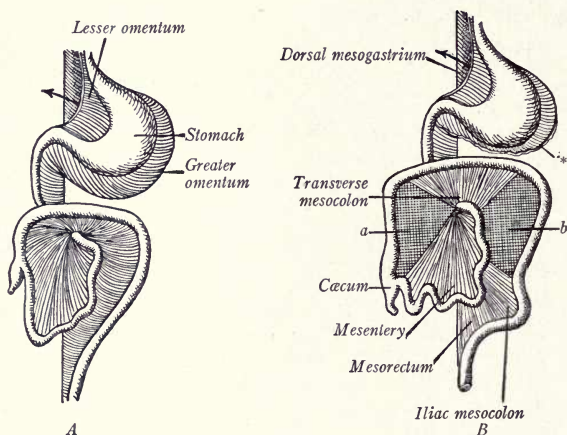


FIG. 203.—Diagram showing the development of the mesenteries in ventral view (modified after Tourneux). *, Cut edge of greater omentum; a, area of ascending mesocolon fused to dorsal body wall; b, area of descending mesocolon fused to dorsal body wall. Arrow in omental bursa.

mesenteric artery as an axis. From this focal point the mesentery of the small intestine and colon spreads out fan-like. The *mesoduodenum* is pressed against the dorsal body wall, fuses with its peritoneal layer, and is obliterated (Fig. 202). Since the transverse colon lies ventral to the duodenum it cannot come into apposition with the body wall; where its mesentery crosses the duodenum it fuses at its base with the surface of the latter and of the pancreas. Its fixed position now being transverse instead of sagittal, the mesentery is known as the *transverse mesocolon*. The mesentery of the ascending colon is flattened against the dorsal body wall on the right and fuses with the peritoneum (Fig. 203). Similarly, the descending mesocolon is applied to the body wall of the left side.

There are thus left free: (1) the transverse mesocolon; (2) the mesentery proper of the jejunum and ileum, with numerous folds corresponding to the loops of the intestine; (3) the iliac mesocolon; (4) the mesorectum, which retains its primitive relations.

Anomalies:—The persistence of a dorsal opening in the diaphragm, more commonly on the left side, finds its explanation in the imperfect development of the pleuro-peritoneal membrane. Such a defect may lead to *diaphragmatic hernia*, the abdominal viscera projecting to a greater or less extent into the pleural cavity. Similarly, faulty development of the left pleuro-pericardial membrane sometimes causes the heart and left lung to occupy a common cavity.

The mesenteries also may show malformations, due to the persistence of the simpler embryonic conditions, usually correlated with the defective development of the intestinal canal. In about 30 per cent of cases the ascending and descending mesocolon are more or less free, having failed to fuse with the dorsal peritoneum. The primary sheets of the greater omentum may also fail to unite, so that the inferior recess extends to the caudal end of the greater omentum.

A striking anomaly is *situs viscerum inversus*, in which the various visceral organs are transposed right for left and left for right, as in a mirror image. An independent transposition of the thoracic or abdominal viscera alone may occur. The larger left great venous trunks are thought to be chiefly responsible for the usual positions of the viscera.

CHAPTER VIII

THE DEVELOPMENT OF THE UROGENITAL SYSTEM

THE excretory and reproductive systems are intimately associated in development. Both arise from the mesoderm of the intermediate cell mass (nephrotome), which unites the primitive segments with the lateral somatic and splanchnic mesoderm (p. 53; Fig. 205).

Vertebrates possess excretory organs of three distinct types. The *pronephros* is the functional kidney of amphioxus and certain lampreys, but appears only in immature fishes and amphibians, being replaced by the *mesonephros*. The embryos of amniotes (reptiles, birds, and mammals) possess first a pronephros, and then a mesonephros, whereas the permanent kidney is a new organ, the *metanephros*. Whether these glands represent modifications of an originally continuous organ, or whether they are three distinct structures, is undecided, but however this may be, the pro-, meso-, and metanephroi of amniotes develop successively in the order named, both as regards time and place.

THE PRONEPHROS

The *pronephros*, when functional, consists of paired, segmentally arranged tubules, one end of each tubule opening into the coelom, the other into a longitudinal pronephric duct which drains into the cloaca (Fig. 204 A). Near the *nephrostome* (the opening into the coelom), knots of arteries project into the coelom, forming *glomeruli*. Fluid from the coelom and glomeruli, and excreta from the cells of the tubules are carried by ciliary movement into the pronephric ducts.

The human pronephros is vestigial. It consists of about seven pairs of rudimentary pronephric tubules, formed as dorsal sprouts from the nephrotomes (Fig. 205) in each segment, from the seventh to the fourteenth, and perhaps from more cranial segments as well. The nodules hollow out and open into the coelom. Dorsally and laterally, the tubules of each side bend backward and unite to form a longitudinal *collecting duct* (Fig. 204 B, A). The tubules first formed in the seventh segment begin to degenerate before those of the fourteenth segment have developed. Caudal to the fourteenth segment no pronephric tubules are developed, but the free end of the collecting duct, by a process of terminal growth, extends caudad beneath the ectoderm and lateral to the nephrogenic cord, until it reaches the lateral wall of the cloaca and perforates it. Thus are

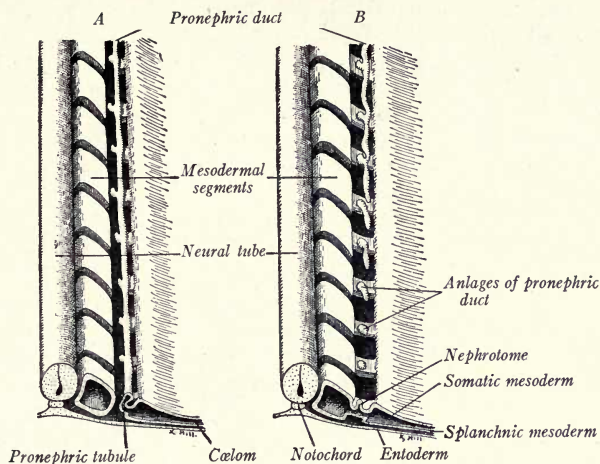


FIG. 204.—Diagrams showing the development of the pronephric duct and pronephric tubules (modified from Felix). A represents a later stage than B.

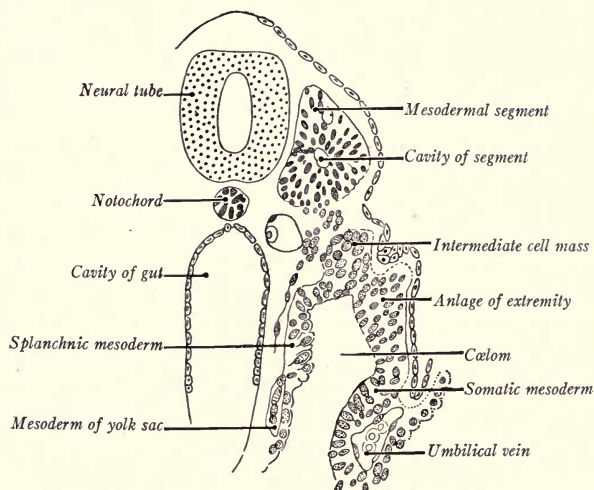


FIG. 205.—Transverse section of a 2.4 mm. human embryo, showing the intermediate cell mass or nephrotome (Kollmann).

formed the paired *primary excretory (pronephric) ducts*. The pronephric tubules begin to appear in embryos of 1.7 mm., with nine or ten primitive segments (Felix); in 2.5 mm. embryos (23 segments) all the tubules have developed and the primary excretory duct is nearly complete. In 4.25 mm. embryos the duct has reached the wall of the cloaca and soon after fuses with it. The pronephric tubules soon degenerate, but the primary excretory ducts persist and become the *ducts of the mesonephroi*, or mid-kidneys.

THE MESONEPHROS

The *mesonephros*, like the pronephros, consists essentially of a series of tubules, each of which at one end is related to a knot of blood vessels and at the other end opens into the primary excretory duct. Besides possessing an internal glomerulus alone they differ from the pronephric tubules in that the nephrostomes are transitory, never opening into the mesonephric chamber. The mesonephric tubules arise just caudal to the pronephros and from the same general source, that is, the nephrotomes. Only a few of the more cranial tubules, however, are formed from distinct intermediate cell masses, for caudal to the tenth pair of segments this mesoderm constitutes unsegmented, paired *nephrogenic cords*. These may extend caudally as far as the twenty-eighth segment. The primary excretory ducts lie lateral to the nephrogenic cords.

When the developing mesonephric tubules begin to expand, there is not room for them in the dorsal body wall and as a result this bulges ventrally into the coelom. Thus, there is produced on either side of the dorsal mesentery a longitudinal *urogenital fold*, which may extend from the sixth cervical to the third lumbar segment (Fig. 220). Later, this ridge is divided into a lateral *mesonephric fold* and into a median *genital fold*, the anlage of the *genital gland*.

Differentiation of the Tubules.—The nephrogenic cord in 2.5 mm. embryos first divides into spherical masses of cells, the anlagen of the *mesonephric tubules*. Four of these may be formed in a single segment. Appearing first in the 13th, 14th and 15th segments, the anlagen of the tubules differentiate both cranially and caudally. In 5.3 mm. embryos the cephalic limit is reached in the sixth cervical segment, and thereafter degeneration begins at the cephalic end (Fig. 207). Hence, the more cranial tubules overlap those of the pronephros. In 7 mm. embryos the caudal limit is reached in the third lumbar segment.

The spherical anlagen of the tubules differentiate in a cranio-caudal direction (Fig. 206). First, vesicles with lumina are formed (4.25 mm.). Next, the vesicles elongate laterally, unite with the primary excretory ducts, and become S-shaped (4.9 mm.). The free, vesicular end of the

tubule enlarges, becomes thin walled, and into this wall grows a knot of arteries to form the *glomerulus* (embryos of 5 to 7 mm.). The tubule, at first solid, hollows out and is lined with a low columnar epithelium. The outer wall of the vesicle about the *glomerulus* is *Bowman's capsule*, the two constituting a *renal corpuscle* of the mesonephros (Fig. 206D). In the human embryo the tubules do not branch or coil as in pig embryos, consequently the mesonephros is relatively smaller. At 10 mm., about 35

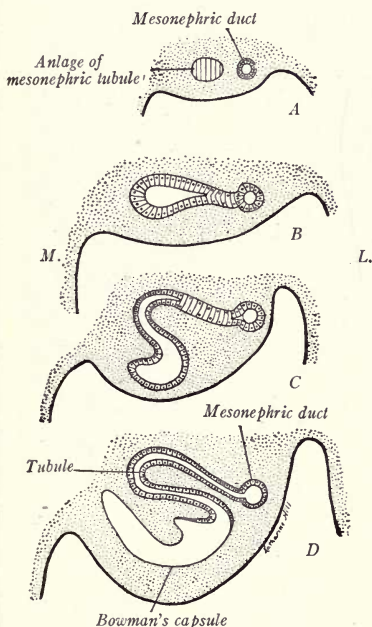


FIG. 206.—Diagrams showing the differentiation of the mesonephric tubules (modified after Felix). L. lateral; M. median.

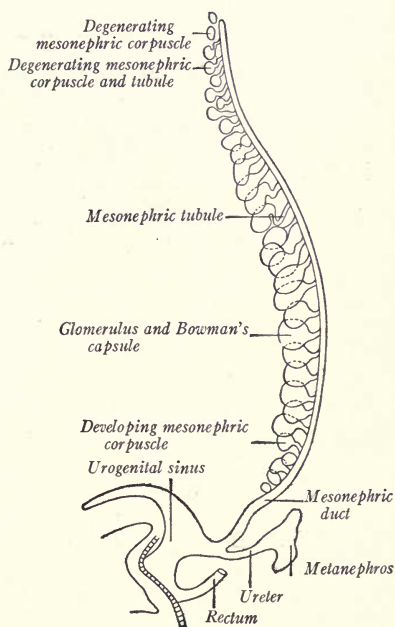


FIG. 207.—Diagram showing the anlagen of the urinary organs in about 10 mm. human embryos, as seen from the left side (based on reconstructions by Keibel and Felix).

tubules are present in each mesonephros and the glomeruli are conspicuous (Fig. 207). Each tubule shows a distal secretory portion and a proximal collecting part which connects with the duct (Fig. 208). The glomeruli form a single median column; the tubules are dorsal and the duct is lateral in position. Ventro-lateral branches from the aorta supply the glomeruli, (Fig. 323), while the posterior cardinal veins (Fig. 72), dorsal in position, break up into a network of sinusoids about the tubules (see Chapter IX).

The primary excretory (Wolffian) duct, or *mesonephric duct*, is solid in 4.25 mm. embryos. A lumen is formed at 7 mm., wider opposite the openings of the tubules. The duct is important, as the ureteric anlage of the permanent kidney grows out from its caudal end, while the duct itself is transformed into the chief genital duct of the male, and its derivatives.

That the human mesonephros is a functional excretory organ is plausible (Bremer, 1916), but not proved. Degeneration proceeds rapidly in embryos between 10 and 20 mm. long, beginning cranially. New tubules are formed at the same time caudally. In all, 83 pairs of tubules arise, of which only 26 pairs persist at 21 mm., and these are usually broken at the angle between the collecting and secretory regions. They are divided into an upper group and a lower group. The collecting portions

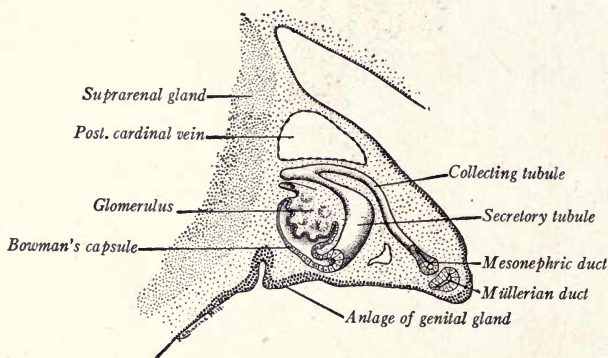


FIG. 208.—Reconstruction of the contents of the urogenital fold, from transverse sections of a 12 mm. human embryo. $\times 95$.

of the upper group, numbering 5 to 12, unite with the rete tubules of the testis or ovary. In the male they form the *effluent ductules* of the epididymis. In the female they constitute the *epoöphoron*. Of the lower group a few tubules persist in the male, as the *paradidymis*. In the female they form the *paroöphoron*.

THE METANEPHROS

The essential parts of the permanent kidney are the *renal corpuscles* (glomerulus with Bowman's capsule), *secretory tubules*, and *collecting tubules*. The collecting tubules open into expansions of the duct, the pelvis and calyces. The duct itself is the ureter, which opens into the bladder. Like the mesonephros, the metanephros is of double origin. The ureter, pelvis, calyces, and collecting tubules are outgrowths of the

mesonephric duct. The secretory tubules and the capsules of the renal corpuscles are differentiated from the isolated caudal end of the nephrogenic cord and thus have a similiar origin as the mesonephric tubules.

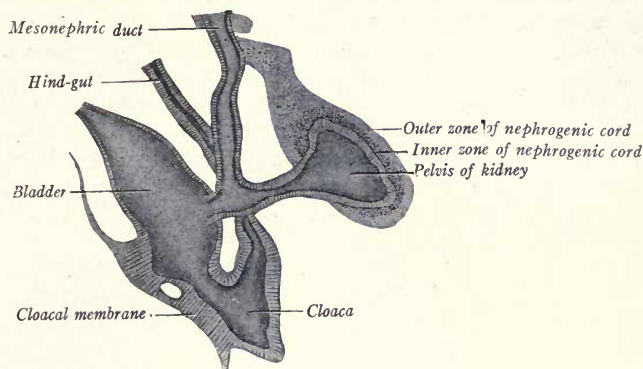


FIG. 209.—Reconstruction of the anlagen of the metanephros in a human embryo of about 9 mm. (after Schreiner).

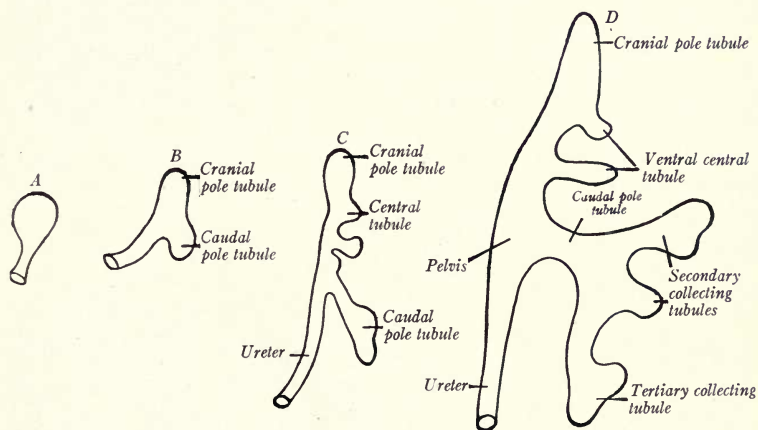


FIG. 210.—Diagrams showing the development of the primitive pelvis, calyces and collecting tubules of the metanephros (based on reconstructions by Schreiner and Felix).

In embryos of about 5 mm. the mesonephric duct makes a sharp bend just before it joins the cloaca, and it is at the angle of this bend that the ureteric evagination appears, dorsal and somewhat median in position (Fig. 216, B, C). The bud grows at first dorsally, then cranially. Its

distal end expands and forms the primitive *pelvis*. Its proximal elongated portion is the *ureter*. The anlage grows into the lower end of the *nephrogenic cord* (Fig. 209), which, in 46 mm. embryos, is separated from the cranial end of the cord at the twenty-seventh segment. The nephrogenic tissue forms a cap about the primitive pelvis, and, as the pelvis grows cranially, is carried along with it. In embryos of 9 to 13 mm. the pelvis, having advanced cephalad through three segments, attains a position in the retroperitoneal tissue dorsal to the mesonephros and opposite the second lumbar segment. Thereafter, the kidney enlarges both cranially and caudally without shifting its position. The ureter elongates as the embryo grows in length. The cranial growth of the kidney takes place dorsal to the suprarenal gland (Fig. 232).



FIG. 211.—Reconstruction of the ureter, pelvis, calyces and their branches from the metanephros of a 16 mm. human embryo (Huber). $\times 50$.

Primary collecting tubules grow out from the primitive pelvis in 10 mm. embryos. Of the first two, one is cranial, the other caudal in position, and between these there are usually two others (Fig. 210 B, C). From an enlargement, the ampulla, at the end of each primary tubule grow out two, three, or four secondary tubules. These in turn give rise to tertiary tubules (Fig. 210 D) and the process is repeated until the fifth month of fetal life, when it is estimated that twelve generations of tubules have been developed. The pelvis and both primary and secondary tubules enlarge during development. The first two primary tubules become the *major calyces*, and the secondary tubules opening into them form the *minor calyces* (Fig. 211). The tubules of the third and fourth orders are taken up into the walls of the enlarged secondary tubules so that the tubules of the fifth

order, 20 to 30 in number, open into the minor calyces as *papillary ducts*. The remaining orders of tubules constitute the *collecting tubules* which form the greater part of the medulla of the adult kidney.

When the four to six primary tubules develop, the nephrogenic cap about the primitive pelvis is subdivided and its four to six parts cover the end of each primary tubule. As new orders of tubules arise, each mass of nephrogenic tissue increases in amount and is again subdivided until finally it forms a peripheral layer about the ends of the branches tributary to a primary tubule. The converging branches of such a tubular 'tree' constitute a primary renal unit, or *pyramid*, with its base at the periphery of the kidney and its apex projecting into the pelvis. The apices of the pyramids are termed *renal papillæ*, and through them the

larger collecting ducts open. The nephrogenic tissue forms the *cortex* of the kidney, and each subdivision of it, covering the tubules of a pyramid peripherally, is marked off on the surface of the organ by grooves or depressions. The human fetal kidney is thus distinctly lobated, the lobations persisting until after birth, a condition which is permanent in reptiles, birds, and some mammals (whale, bear, ox). The primary pyramids are subdivided into several secondary and tertiary pyramids. Between the pyramids the cortex of nephrogenic tissue dips down to the pelvis, forming the *renal columns* (of Bertin). The collecting tubules, on the other hand, extend out into the cortex as the cortical rays, or *pars radiata* of the cortex. In these rays, and in the medulla of the kidney, the collecting tubules run parallel and converge to the papillæ.

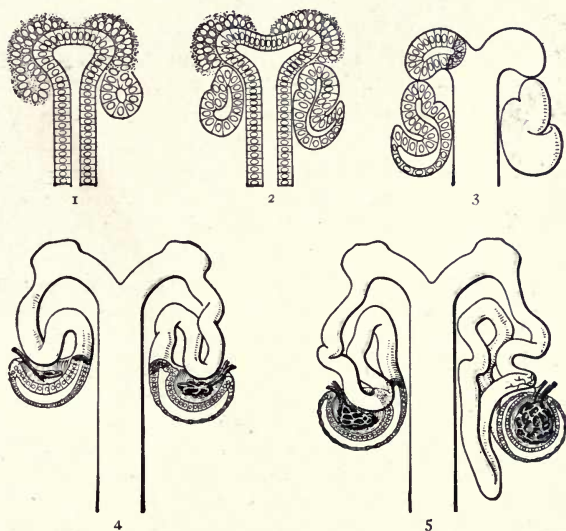


FIG. 212.—Semidiagrammatic figures of the anlage and differentiation of renal vesicles and early developmental stages of uriniferous tubules of mammals. 1 and 2, Anlage and successive stages in the differentiation of renal vesicles, as seen in sagittal sections; 3, section and outer form of tubular anlage before union with collecting tubule at the beginning of S-shaped stage; 4 and 5, successive stages in the development of the tubules, Bowman's capsule, and glomerulus beginning with a tubular anlage showing a well-developed S-shape (Huber).

Differentiation of the Nephrogenic Tissue.—In stages from 13 to 19 mm., the nephrogenic tissue about the ends of the collecting tubules condenses into spherical masses that lie in the angles between the buds of new collecting tubules and their parent stems (Fig. 212). One such metanephric sphere is formed for each new tubule. The spheres are con-

verted into vesicles with eccentrically placed lumina. The vesicle elongates, its thicker outer wall forming an S-shaped tubule which unites with a collecting tubule, its thin inner wall becoming the capsule (Bowman's) of a renal corpuscle. The uriniferous tubules of the adult kidney have a definite and peculiar structure and arrangement (Fig. 213 A). Beginning with a renal corpuscle, each tubule forms a *proximal convoluted portion*, a *U-shaped loop* (of Henle) with *descending* and *ascending limbs*, a *connecting*

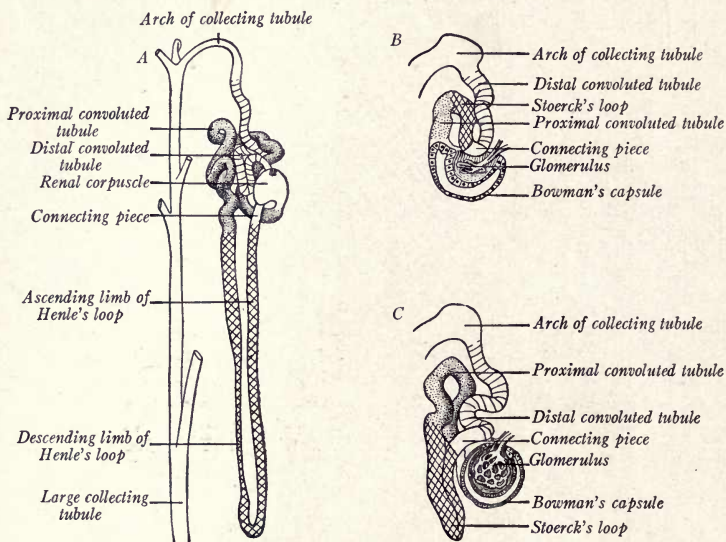


FIG. 213.—Diagrams showing the differentiation of the various parts of the uriniferous tubules of the metanephros (based on the reconstructions of Huber and Stoerck): A, From an adult human kidney; B, C, from human embryos.

piece, which lies close to the renal corpuscle, and a *distal convoluted portion* continuous with the collecting tubule. These parts are derived from the S-shaped anlage, which is composed of a lower, middle and upper limb. The middle limb, somewhat U-shaped, bulges into the concavity of Bowman's capsule (Fig. 213 B). By differentiation the lower portion of the lower limb becomes Bowman's capsule, ingrowing arteries forming the glomerulus (Fig. 213 B, C). The upper part of the same limb by enlargement, elongation, and coiling becomes the proximal convoluted tubule. The neighboring portion of the middle limb forms the primitive loop (of Stoerck); the base of the middle limb gives rise to the connecting piece, and the rest of it, with the upper limb of the S, forms the distal convoluted

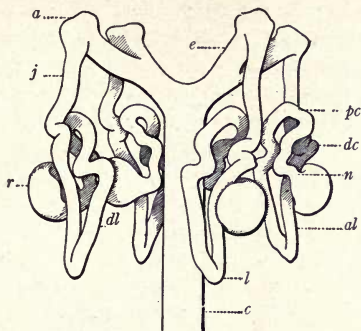


FIG. 214.—Diagram showing the relation of Bowman's capsule and the uriniferous tubules to the collecting tubules of the metanephros (Huber). *c*, Collecting tubules; *e*, end branches of collecting tubules; *r*, renal corpuscles; *n*, neck; *pc*, proximal convoluted tubule; *dl*, descending limb of Henle's loop; *l*, *al*, ascending limb of Henle's loop; *dc*, distal convoluted tubule; *j*, junctional tubule.

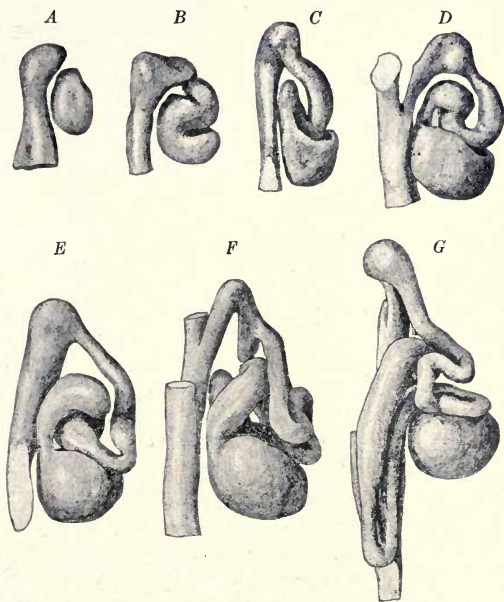


FIG. 215.—Several stages in the development of the uriniferous tubules and glomeruli of the human metanephros of the seventh month (reconstructions by Huber). $\times 160$.

tubule (intermediate piece of Felix). The primitive loop of Stoerck includes both the ascending and descending limbs of Henle's loop and a portion of the proximal convoluted tubule. Henle's loop is differentiated during the fourth fetal month (Toldt) and extends from the pars radiata of the cortex into the medulla (Fig. 214). The concavity of Bowman's capsule, into which grow the arterial loops of the glomerulus, is at first shallow. Eventually the walls of the capsule grow about and enclose the vascular knot, except at the point where the arteries enter and emerge (Fig. 212, 4 and 5). Renal corpuscles are first fully formed in 28 to 30 mm. embryos. The new corpuscles are formed peripherally from persisting nephrogenic tissue until the tenth day after birth, hence in the adult the oldest corpuscles are those next to the medulla. Reconstructions of the various stages in the development of the uriniferous tubules are shown in Fig. 215.

Renal Arteries.—Bremer (1915) derives the renal arteries not from transformed mesonephric vessels, as did Broman (1906), but from a periaortic plexus of multiple aortic origin. The mechanical selection of permanent channels explains the frequent variations in the renal vessels.

Anomalies.—The kidneys may fail to ascend from their embryonic position in the pelvis. Absence of one kidney is not infrequent. The kidneys sometimes fuse, either completely into a disc-shaped mass, or partially by cortical union ('horse-shoe kidney'); in such cases the ducts usually are bilateral. Double or cleft ureters and pelves occur. 'Cystic kidney' results when the uriniferous tubules fail to unite with the collecting tubules.

DIFFERENTIATION OF THE CLOACA, BLADDER, URETHRA AND UROGENITAL SINUS

In embryos of 1.4 mm., the cloaca, a caudal expansion of the hind-gut, is in contact ventrally with the ectoderm, and ectoderm and entoderm together form the *cloacal membrane* (Fig. 216 A). Ventro-cephalad, the cloaca gives off the allantoic stalk. At a somewhat later stage, the cloaca receives laterally the mesonephric ducts and is prolonged caudally as the tail-gut (Fig. 216 B).

In embryos of 5 mm., the ureteric anlagen of the metanephroi are present as buds of the mesonephric ducts (Fig. 216 C, D). Next, the saddle-like partition between the intestine and allantois grows caudally, dividing the cloaca into a dorsal *rectum* and ventral, primitive *urogenital sinus*. The division is complete in embryos of 11 to 15 mm., and at the same time the partition, fusing with the cloacal membrane, divides it into the *anal membrane* of the gut and the *urogenital membrane*. At 11 mm., according to Felix, the primitive urogenital sinus by elongation and constriction is differentiated into two regions: (1) a dorsal vesico-urethral anlage which receives the allantois and mesonephric duct, and is connected by the constricted portion with (2) the phallic portion of the urogenital

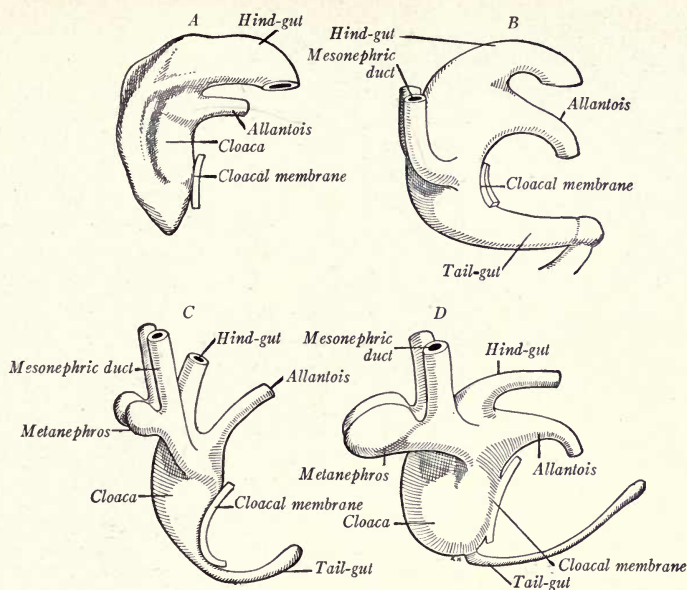


FIG. 216.—Four stages showing the differentiation of the cloaca into the rectum, urethra and bladder (after reconstructions by Pohlman). \times about 50. A, from a human embryo of 3.5 mm.; B, at about 4 mm.; C, at 5 mm.; D, at 7 mm.

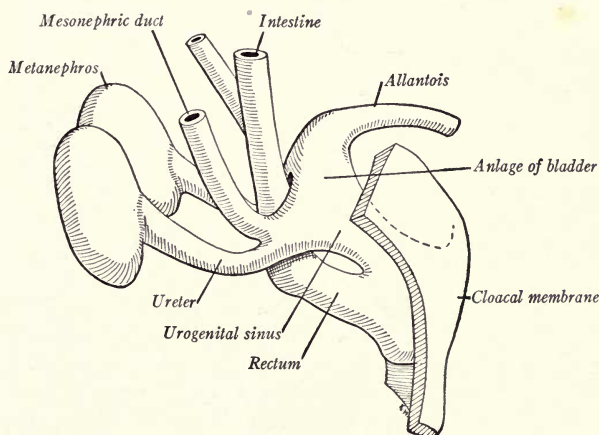


FIG. 217.—Reconstruction from a 12 mm. human embryo, showing the partial subdivision of the cloaca into rectum and urogenital sinus (after Pohlman). \times 65.

sinus (Figs. 217 and 218). The latter extends into the phallus of both sexes and forms a greater part of the urethra (Fig. 219); its fate is described on p. 226 in connection with the external genitalia.

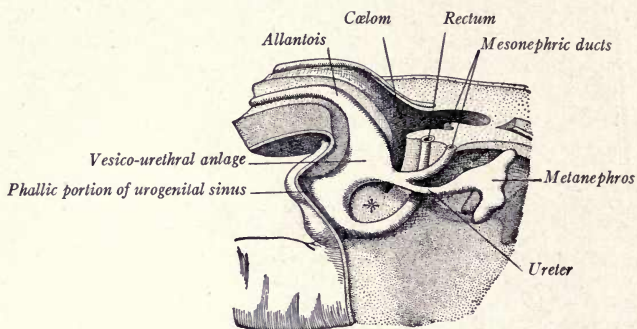


FIG. 218.—Reconstruction of the caudal portion of an 11.5 mm. human embryo, showing the differentiation of the rectum, bladder and urethra (after Keibel's model). $\times 25$.

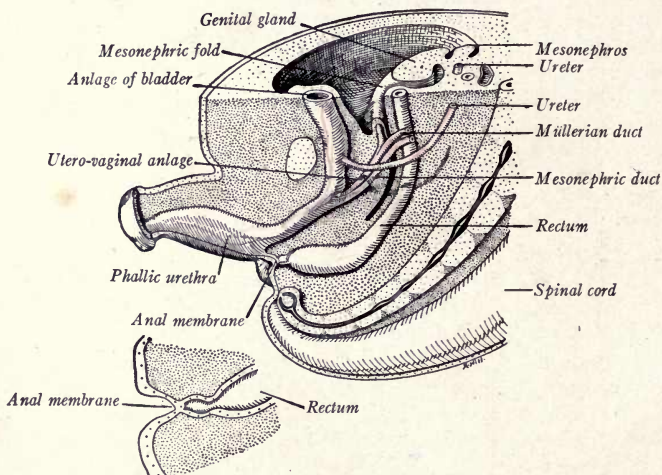


FIG. 219.—Reconstruction of the caudal end of a 29 mm. human embryo, showing the complete separation of the rectum and urogenital sinus and the relations of the urogenital ducts (after Keibel's model). $\times 15$.

The vesico-urethral anlage enlarges and forms the *bladder* and a portion of the urethra. In 7 mm. embryos the proximal ends of the mesonephric ducts are funnel shaped, and, at 10 mm., with the enlargement of the bladder, these ends are taken up into its wall until the ureters and meso-

nephric ducts acquire separate openings. The ureters, having previously shifted their openings into the mesonephric ducts from a dorsal to lateral position, now open into the vesico-urethral anlage lateral to the mesonephric ducts. The lateral walls of the bladder anlage grow more rapidly than its dorso-median urethral wall, hence the ureters are carried cranially and laterally upon the wall of the bladder, while the mesonephric ducts, now the male ducts, open close together on a hillock, *Müller's tubercle*, into the dorsal wall of the urethra (Fig. 219).

Thus a triangular area, roughly bounded by the openings of the ureters and ejaculatory ducts, is of mesodermal origin. The narrowed apex of the bladder, continuous with the allantoic stalk at the umbilicus, is known as the *urachus*. It persists as the solid, fibrous *ligamentum umbilicale medium*. Contrary to earlier views, the allantois contributes nothing to the bladder or urachus (Felix, 1912).

The transitional epithelium of the bladder appears at 60 mm. (C H). The outer longitudinal layer of smooth muscle develops in 22 mm. embryos, and, in 26 mm. embryos, the circular muscle appears. The inner longitudinal muscle layer is found at 55 mm. (C H) and the sphincter vesicæ in fetuses of 90 mm. (C H).

Anomalies.—A conspicuous malformation is that of a persistent cloaca, due to the failure of the rectum and urogenital sinus to separate. The bladder sometimes opens widely onto the ventral body wall and is everted through the fissure; a urogenital aperture corresponding to the upper extent of the primitive cloacal membrane (Fig. 216, C, D) would cause this condition. At times, the urachus remains a patent tube, opening at the umbilicus. Portions of its epithelium which fail to degenerate may form cysts.

THE GENITAL GLANDS AND DUCTS

A. INDIFFERENT STAGE

In origin and early development, the ovary and testis are identical. The *urogenital fold* (p. 198) is the anlage of both the mesonephros and the genital gland (Figs. 122 and 220). At first two-layered, its epithelium in embryos of 5 mm. thickens over the ventro-median surface of the fold, becomes many-layered, and bulges into the coelom ventrally, producing the longitudinal *genital fold* (Fig. 208). The genital fold thus lies mesial and parallel to the mesonephric fold. Large *primordial germ cells* are found in 2.5 mm. embryos in the entoderm of the future intestinal tract (Fuss). At 3.5 mm. they migrate into the dorsal mesenteric epithelium and thence into the epithelium of the genital fold. It is probable that the definitive germ cells of the genital glands are descendants of these elements. At 10 to 12 mm. the genital anlage shows no sexual differentiation (Fig. 221). There is a superficial *epithelial layer* and an *inner epithelial mass* of somewhat open structure.

Owing to the great development of the suprarenal glands and metanephroi, the cranial portions of the urogenital folds, at first parallel and close together, are displaced laterally. This produces a double bend in each fold, which, in 20 mm. embryos, shows a *cranial longitudinal portion*, a

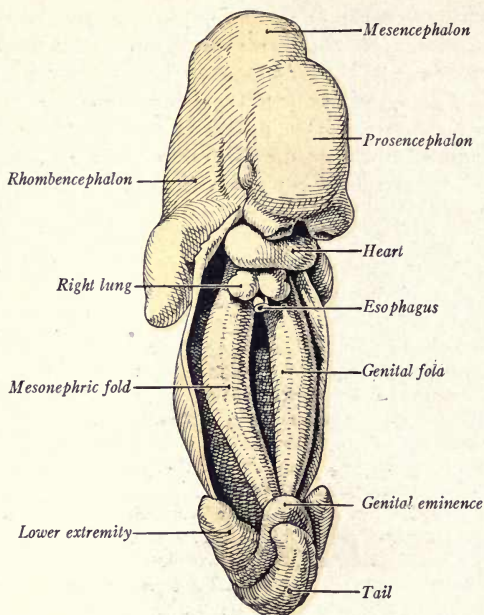


FIG. 220.—Ventral view of the urogenital folds in a human embryo of 9 mm. (Kollmann).

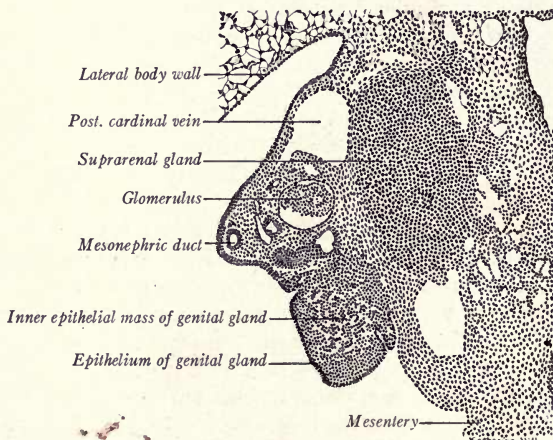


FIG. 221.—Transverse section through the mesonephros, genital gland and suprarenal gland of the right side; from a 12 mm. human embryo. $\times 165$.

transverse middle portion between the bends; and a longitudinal caudal portion (Fig. 238 A). In the last named segment, the mesonephric ducts course to the cloaca, and here the right and left folds fuse, producing the genital cord (Fig. 232). As the genital glands increase in size they become constricted from the mesonephric fold by lateral and mesial grooves until the originally broad base of the genital fold is converted into a stalk (Figs. 225 to 227). This stalk-like attachment extends lengthwise and forms in the male the *mesorchium*, in the female the *mesovarium*. The urogenital fold is, at the same time, constricted from the dorsal body wall until it is attached only by a narrow mesentery which eventually forms either the *ligamentum testis* or *ligamentum ovarii*.

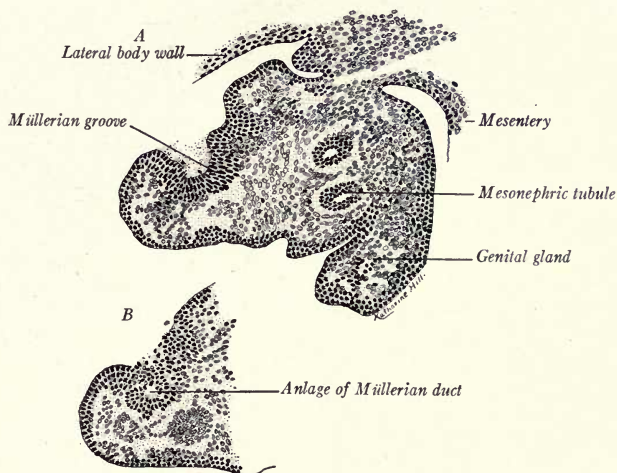


FIG. 222.—Transverse sections through the anlage of the right Müllerian duct from a 10 mm. human embryo. $\times 250$. A, showing the groove in the urogenital epithelium; B, three sections caudad, showing the tubular anlage of the duct.

Indifferent Stage of the Genital Ducts.—The *mesonephric ducts*, with the degeneration of the mesonephroi, become the male genital ducts. In both sexes there also develop a pair of female ducts (of Müller). In embryos of 10 mm. these *Müllerian ducts* develop as ventro-lateral thickenings of the urogenital epithelium at the level of the third thoracic segment and near the cranial ends of the mesonephroi. Next, a ventro-lateral groove appears in the epithelium of the mesonephric fold (Fig. 222 A). Caudally, the dorsal and ventral lips of the groove close and form a tube which separates from the epithelium and lies beneath it (Fig. 222 B). Cranially, the tube remains open as the funnel-shaped *ostium abdominale* of the Müllerian

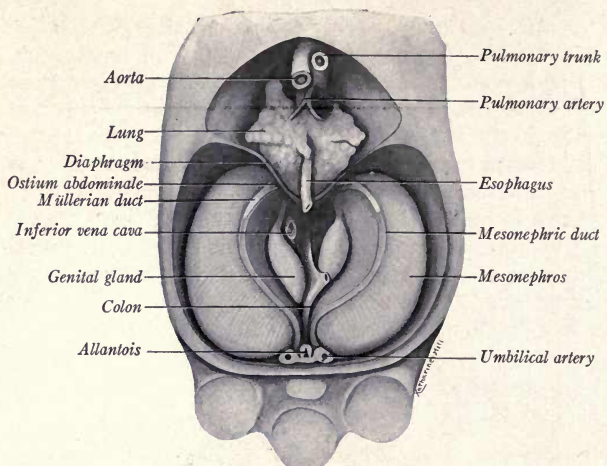


FIG. 223.—Ventral dissection of an 18 mm. pig embryo, to show the anlagen of the Müllerian ducts. $\times 7$.

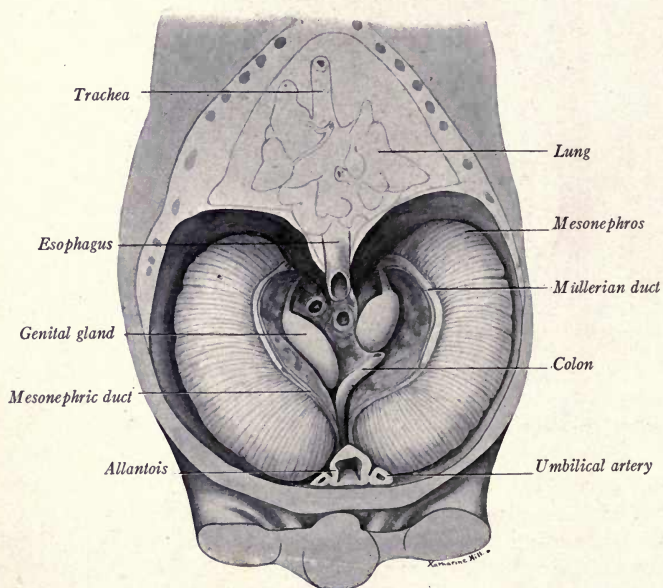


FIG. 224.—Ventral dissection of a 24 mm. pig embryo, showing the anlagen of the Müllerian ducts at a later stage of development than in Fig. 223. $\times 6$.

duct. The solid end of the tube grows caudalward beneath the epithelium, lateral to the mesonephric, or male ducts (Figs. 223 to 225). Eventually, by way of the genital cord, the Müllerian ducts reach the median dorsal wall of the *urogenital sinus* and open into it (Figs. 219 and 238 A). Their further development into uterine tubes, uterus, and vagina is described on page 220. Embryos not longer than 12 mm. are thus characterized by the possession of indifferent genital glands and both male and female genital ducts. There is as yet no sexual differentiation. The development and position of the Müllerian ducts is well shown in ventral dissections of pig embryos (Figs. 223 and 224); the mesonephroi of the pig are much larger than in man. In the lowest vertebrates the Müllerian duct arise by a longitudinal splitting of the mesonephric duct.

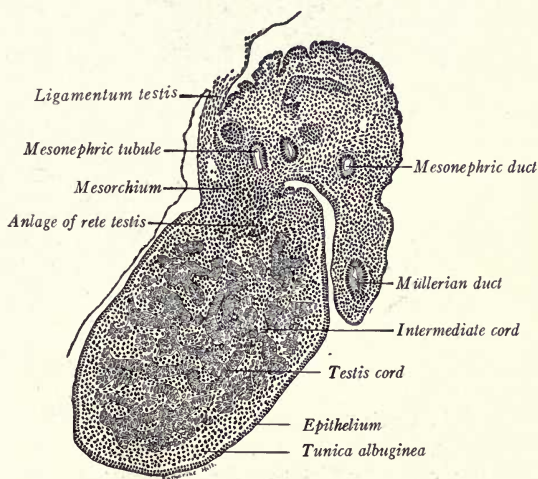


FIG. 225.—Transverse section through the left testis and mesonephros of a 20 mm. human embryo. $\times 250$.

B. INTERNAL SEXUAL TRANSFORMATIONS

Differentiation of the Testis.—In the male embryos of 13 mm. the genital glands show two characters which mark them as testes: (1) the occurrence of branched, anastomosing cords of cells, the *testis cords*; (2) the occurrence between epithelium and testis cords of a layer of tissue, the anlage of the *tunica albuginea* (Fig. 225). According to Felix (1912), the testis cords of man are developed suddenly from the loose, inner epithelial mass by a condensation of its cells. The cords converge and grow smaller towards the mesorchium, where they form the dense, epithelial anlage

of the *rete testis*. Two or three layers of loosely arranged cells between the testis cords and the epithelium constitute the anlage of the *tunica albuginea*. On the contrary, Allen (1904) holds that the testis cords of the rabbit and pig are formed as invaginations of the surface epithelium.

The testis cords soon become rounded and are marked off by connective-tissue sheaths from the *intermediate cords*, columns of undifferentiated tissue which lie between them (Fig. 226). Toward the rete testis the sheaths of the testis cords unite to form the anlage of the *mediastinum testis*. The testis cords are composed chiefly of *indifferent cells* with a few larger *germ cells*. The cells gradually arrange themselves radially about the inside of the connective-tissue sheath as a many-layered epithelium, in which, during the seventh month, a lumen appears. The lumina appear in the

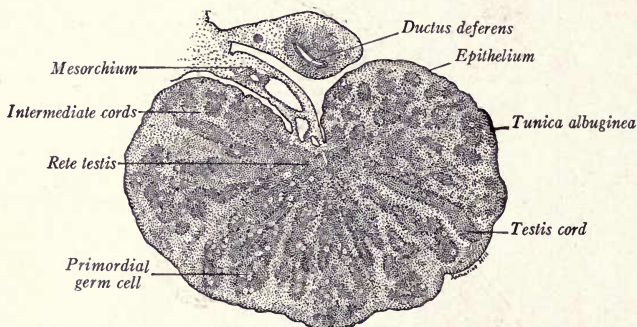


FIG. 226.—Section through the testis of a 100 mm. human fetus. $\times 44$.

peripheral ends of the testis cords, and, extending toward the rete testis, meet lumina which have formed there. Thus the solid cords of both are converted into tubules. The distal portions of the testis tubules anastomose and form the *tubuli contorti*. Their proximal portions remain straight, as the *tubuli recti*. The rete testis becomes a network of small tubules that finally unite with the collecting tubules of the mesonephros (see p. 219).

The primordial germ cells of the testis cords form the *spermatogonia* of the spermatogenic tubules, and from these at puberty are developed the later generations of spermatogonia (p. 14). The indifferent cells of the tubules become the *sustentacular cells* (of Sertoli) of the adult testis. Certain cells of the intermediate cords, epithelial in origin, are transformed into large, pale cells, which, after puberty, are numerous in the interstitial connective tissue and hence are called *interstitial cells*. The *intermediate cords*, as such, disappear, but the connective-tissue sheaths of the tubules.

unite to form *septula* which extend from the mediastinum testis to the *tunica albuginea*. The latter becomes a relatively thick layer in the adult testis and is so called because of its whitish appearance.

Differentiation of the Ovary.—The primitive ovary, like the testis, consists of an *inner epithelial mass* bounded by the parent peritoneal epithelium. The ovarian characters appear much more slowly than those of the testis. In fetuses of 50 to 80 mm. (C H), the inner epithelial mass, composed of indifferent cells and primordial germ cells, becomes less dense centrally and bulges into the mesovarium (Fig. 227). There may be distinguished a dense, outer cortex beneath the epithelium, a clearer medul-

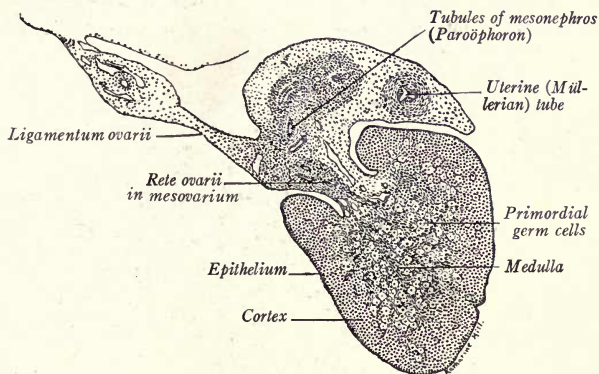


FIG. 227.—Section of an ovary from a 65 mm. human fetus. $\times 44$.

lary zone containing large germ cells, and a dense, cellular anlage in the mesovarium, the primitive *rete ovarii*, which is the homologue of the rete testis. No *epithelial cords* and no *tunica albuginea* are developed at this stage, as in the testis.

Later, three important changes take place: (1) There is an ingrowth of connective tissue and blood vessels from the hilus, resulting in the formation of a *mediastinum* and *septulae*. (2) Most of the cells derived from the inner epithelial mass are transformed into young ova, the process extending from the *rete ovarii* peripherally (Fig. 227). (3) In fetuses of from 80 to 180 mm. (C R) length, the ovary grows rapidly, owing to the formation of a new peripheral zone of cells, derived perhaps in part from the peritoneal epithelium. At the end of this period the *septulae* line the epithelium with a fibrous sheath, the anlage of the *tunica albuginea*. Hereafter, although folds of the epithelium are formed, they do not penetrate beyond the *tunica albuginea*, and all cells derived from this source subsequently degenerate. This new peripheral zone, according to Felix, is always a

single cellular mass in man, cords, or 'Pflüger's tubes,' never growing in from the epithelium. Generally it has been believed that the primary follicles are derived from the subdivision of such cords.

Coincident with the origin of a new zone of cells at the periphery of the ovary, goes the degeneration of young ova in the medulla. By the ingrowth into this region of connective tissue, the ova are separated into clusters, or cords, the genital cells of which all degenerate, leaving in the

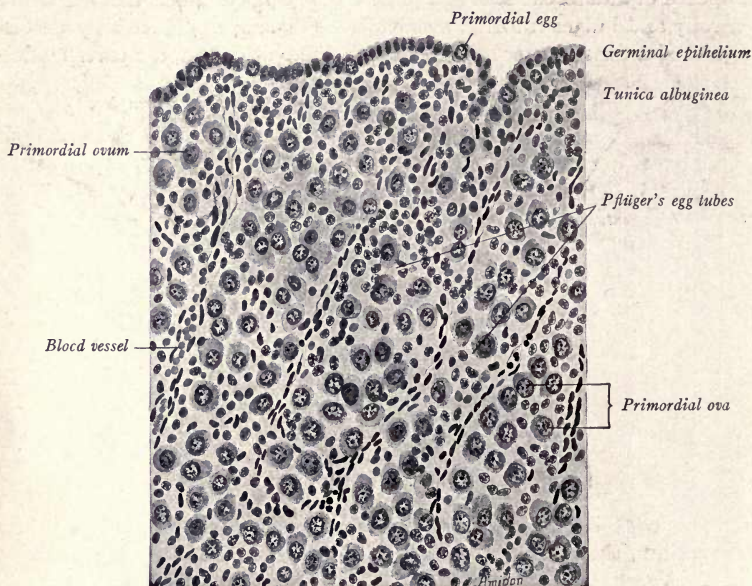


FIG. 228.—Ovary of five-months' fetus, showing primordial follicles (De Lee).

medulla only a *stroma* of connective tissue. Late in fetal life, indifferent cells, by surrounding the young ova of the cortex, produce *primordial follicles* (Fig. 229 A). During the first year after birth the primitive follicles are transformed into *vesicular* (*Graafian*) *follicles*. By cell division, the follicle cells form a zone many layers deep about the young ovum (Fig. 229 B). Next, a cavity appears in the sphere of follicle cells; it enlarges, and produces a vesicle filled with fluid (Figs. 4 and 230). The ovum is now located eccentrically and the follicle cells directly surrounding it constitute the *cumulus oöphorus* (egg-bearing hillock). About the *stratum granulosum*, formed by the original follicle cells, there is differentiated from the stroma of the ovary the *theca folliculi*. This is composed

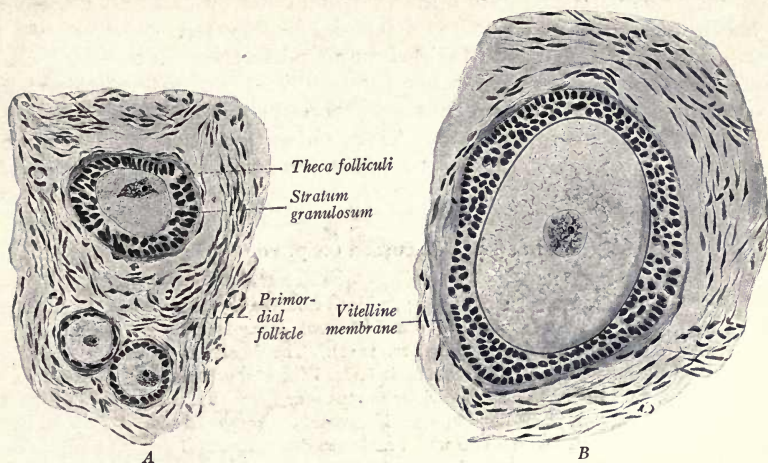


FIG. 229.—Primordial ova and early stages in the development of the Graafian follicle (De Lee).

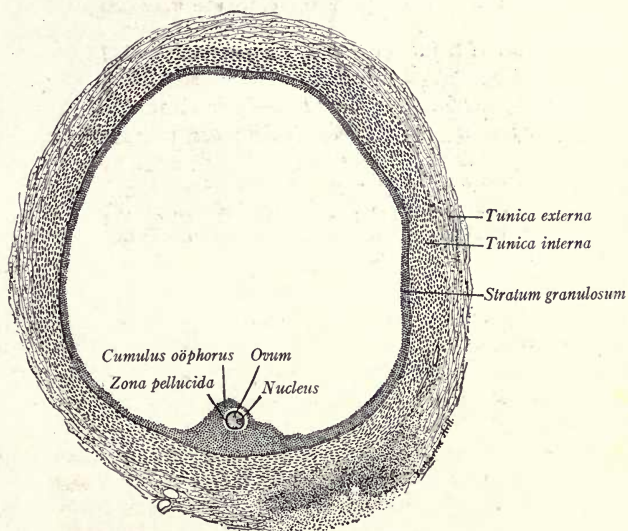


FIG. 230.—Graafian follicle and ovum from the ovary of a fifteen-year-old girl. $\times 30$.

of an inner, vascular *tunica interna* and an outer, fibrous and muscular *tunica externa*.

Fully formed Graafian follicles are found in the ovaries during the second year and they may be even present before birth. Ovulation may occur at this time, but usually these precociously formed follicles degenerate with their contained ova. Thus, although thousands of ova are produced in the ovary, comparatively few are set free ready for fertilization during the sexually active life of the female, from puberty to the climacteric period, or menopause. The details of ovulation and its relation to menstruation has been discussed on p. 10.

The Corpus Luteum.—After ovulation, a blood clot, the *corpus hemorrhagicum*, forms within the empty follicle. The follicle cells of the *stratum granulosum* proliferate, enlarge, and produce a yellow pigment (R. Meyer, 1911). The whole structure, composed of lutein cells and connective tissue strands, is termed the *corpus luteum*, or yellow body. The blood clot is resorbed and replaced by fibrous scar tissue, white in color, known as the *corpus albicans*. If pregnancy does not intervene, the *corpus luteum spurium* reaches its greatest development within two weeks and then degenerates. In cases of pregnancy the *corpus luteum verum* continues its growth until, at the thirteenth week, it reaches a maximal diameter of 15 to 30 mm.; at birth it is still a prominent structure in the ovary. It is believed to produce an important internal secretion, for if the corpus luteum is removed the ovum fails to attach itself to the wall of the uterus, or if already embedded, development ceases (Fraenkel). An influence in retarding ovulation and stimulating the mammary gland function has also been shown experimentally (L. Loeb; O'Donoghue).

Comparison of the Testis and Ovary.—It is clear that the superficial epithelium, after forming the inner epithelial mass, takes no further part in the differentiation of the testis and only a small part, if any, in that of the ovary. The testis cords, rete testis, and tunica albuginea differentiate early from the inner epithelial mass. The inner epithelial mass of the ovary develops slowly and passively being divided and moulded by actively ingrowing connective tissue. The Graafian follicles are not the homologues of the testis cords, and the tunica albuginea appears late. The rete ovarii corresponds to the rete testis, but remains a rudimentary structure.

Anomalies.—Congenital absence or duplication of the testes and ovaries is very rare. Fused testes and lobed ovaries are also known.

Teratomata.—These peculiar tumor-like growths occur rather frequently in the ovary, less often in the testis and other regions. The simpler types, called *dermoid cysts*, contain ectodermal derivatives such as skin, hair, nails, teeth, and sebaceous glands. They grade into complexes consisting of organ-like masses, from all three germ layers, intermingled without order. Misshapen representatives of all tissues and organs may be present. Among other explanations of the cause, the isolation and subsequent faulty development of blastomeres has been advanced.

Transformation of the Mesonephric Tubules and Ducts.—In both male and female embryos of 21 mm. the mesonephros has degenerated until only twenty-six tubules at most persist, and these are separated into a cranial and a caudal group. In the cranial group of 5 to 12 tubules the collecting portions have separated from the secretory portions. The free ends of these collecting tubules project against that part of the inner epithelial mass which gives rise to the rete tubules of either testis or ovary (Figs. 225 and 227). The cords of the rete develop in contact with the collecting tubules of the mesonephros and unite with them in fetuses of 60 mm. (C H).

In the *male*, the lumina of rete and collecting tubules become continuous and the cranial group of the latter are transformed into the *ductuli efferentes* of the epididymis. During the fifth month of pregnancy the ductuli efferentes coil at their proximal ends, and when surrounded by connective tissue they are known as *lobuli epididymidis*. The lower group of collecting tubules persist as the vestigial *paradidymis* and *ductuli abberantes* (Fig. 238 C).

The efferent ductules convey spermatozoa from the testis tubules into the mesonephric duct, which thus becomes the male genital duct. The cranial portion of the mesonephric duct coils and forms the *ductus epididymidis*; its blind cranial end persists as the *appendix epididymidis*. The caudal portion of the male duct remains straight, and, as the *ductus deferens*, extends from the epididymis to the urethra. Near its opening into the latter it dilates to form the *ampulla*, from the wall of which is evaginated the sacculated *seminal vesicle* in fetuses of 60 mm. (C H).

The epithelium of the genital duct is at first a single layer of columnar cells which form non-motile cilia at 70 mm. (C H). Quite late in development the surrounding mesenchyma gives rise to the muscular layers.

In the *female*, the rete ovarii is always a rudimentary structure, yet some time before birth it becomes tubular and unites with the cranial persisting group of mesonephric collecting tubules which forms a rudimentary structure, the *epoöphoron* (Fig. 238 B). The epithelial cells of the latter become ciliated, and smooth muscle tissue is developed corresponding to that of the epididymis. The caudal group of mesonephric tubules constitute the *paroöphoron*. Usually the greater part of the male genital ducts atrophy in the female, the process beginning at 30 mm. Thus the tubules of the epoöphoron are left without an outlet. Portions of the mesonephric ducts persist as (*Gartner's*) *ducts of the epoöphoron*.

Gartner's ducts may extend as vestigial structures from these epoöphoron to the lateral walls of the vagina, passing through the broad ligament and the wall of the uterus. They open into the vagina close to the free border of the hymen (R. Meyer). The ducts are rarely present throughout their entire length and are absent in two-thirds to three-quarters of the cases examined.

Transformation of the Müllerian Ducts.—The Müllerian, or female ducts, after taking their origin as described on p. 211, grow caudally, following the course of the mesonephric ducts (Fig. 224). At first lateral in position, the Müllerian ducts cross the mesonephric ducts and enter the genital cord median to them (Fig. 238 A). In embryos of 20 to 30 mm. their caudal ends are dorsal to the urogenital sinus, extending as far as the Müllerian tubercle, a projection into the median dorsal wall of the vesico-urethral anlage formed by the earlier entrance of the mesonephric ducts (Fig. 219). This tubercle marks also the position of the future *hymen*. In fetuses of 70 mm. (C H) the Müllerian ducts break through the wall of the urethra and open into its cavity. Before this takes place, the caudal ends of the Müllerian ducts, which are pressed close together between the mesonephric ducts in the genital cord, fuse, and in both male and female embryos of 20 to 30 mm. give rise to the unpaired anlage of the *uterus* and *vagina* (Figs. 219 and 231 A). The paired cranial portions of the Müllerian ducts become the *uterine tubes*. During development the ostial ends of the uterine tubes undergo a true descensus from the third thoracic to the fourth lumbar vertebra.

In the male, these parts are rudimentary. Those portions of the Müllerian ducts corresponding to the uterine tubes and uterus begin to degenerate at 30 mm. The vaginal portions remains as a pouch on the dorsal wall of the urethra, the *vagina masculina*, or *prostatic utricle*. The older term, *uterus masculinus*, is obviously a misnomer which should be abandoned. The extreme cranial end of each Müllerian duct persists as an *appendix testis* (Fig. 238 C).

The Uterus and Vagina.—Since the Müllerian ducts develop in the urogenital folds, they make two bends in their course (Fig. 231 A) corresponding to those of the folds (p. 209). Each consists of a cranial longitudinal portion, a middle transverse portion, and a caudal longitudinal portion which is fused with its fellow to form the *utero-vaginal anlage*. At the angle between the cranial and middle portions is attached the *inguinal fold*, the future *round ligament* of the uterus (Figs. 232 and 233). The mesenchyma condenses about the utero-vaginal anlage and the middle transverse portion of the Müllerian ducts, forming a thick, sharply defined layer, from which is differentiated the muscle and connective tissue of the uterus and vagina (Fig. 231 B). As development proceeds, the cranial wall between the transverse portions of the Müllerian ducts bulges outward, so that its original cranial concavity becomes convex (Fig. 231 B). The middle, transverse portions of the ducts are thus taken up into the wall of the uterus forming its *fundus*, while the narrow *cervix* of the uterus and the *vagina* arise from the utero-vaginal anlage. Through the differentiation of its mesenchymatous wall, the uterus is first brought into relation with the round ligament.

The Hymen.—At the point where the utero-vaginal anlage breaks through the wall of the urogenital sinus there is present the tubercle of Müller that marks the lower limits of the vagina. The tubercle is compressed into a disk, lined internally by the vaginal epithelium, externally by the epithelium of the urogenital sinus, or future *vestibule*. These layers, with the mesenchyma between them, constitute the *hymen*, which thus guards the opening into the vagina (Fig. 238 A, B). A circular aperture in the hymen is for a time closed by a knob of epithelial cells, but later when the hymen becomes funnel-shaped the opening is compressed laterally to form a sagittal slit, the *ostium vaginae*. Müller's tubercle persists in the male as the *colliculus seminalis*, from the summit of which leads off the prostatic utricle.

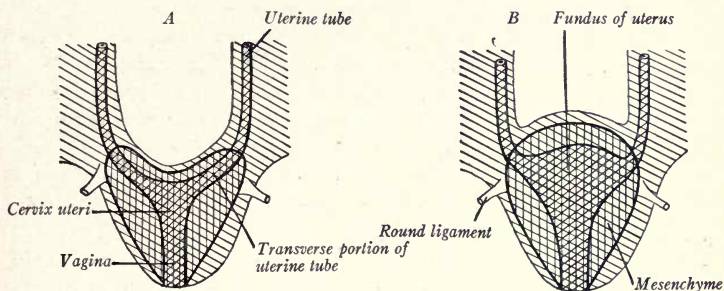


FIG. 231.—Diagrams showing the development of the uterus and vagina (modified after Felix).

Growth of the Uterus.—The uterus shortens one-third soon after birth and does not fully recoup this loss until the eleventh year. The virginal size is attained by a short period of rapid growth, chiefly before puberty.

At 80 mm. (C R) the mucosa and muscularis may be distinguished. The first circular muscle fibers appear in 180 mm. (C R) fetuses; the other muscle layers develop later. The epithelium of the uterine tubes and the fundus of the uterus remains simple; that of the cervix and vagina becomes stratified (38 mm., C R). The tubular fundus glands of the uterus may not appear until near puberty. The vagina is at first without a lumen; from the third to the sixth months of fetal life, dorsal and ventral solid outgrowths of epithelium form its fornices. The vaginal lumen appears in fetuses of 150 to 200 mm. (C R), arising by the degeneration of the central epithelial cells.

Anomalies.—Many cases of abnormal uterus and vagina occur. The more common anomalies are: (1) Complete duplication of the uterus and vagina due to the failure of the Müllerian ducts to fuse. (2) Uterus bicornis, due to the incomplete fusion of the ducts. Combined with these defects, the lumen of the uterus and vagina may fail, partly or completely, to develop and the vaginal canal may not open to the exterior (imperforate hymen). (3) The body of the uterus may remain flat (uterus planifundus; Fig. 231 A) or may fail to grow to normal size (uterus fetalis and infantilis). (4) Congenital absence of one or both uterine tubes, or of the uterus or vagina rarely occurs, but may be associated with hermaphroditism of the external genitalia. The hymen is of variable shape and may be imperforate.

Ligaments of the Internal Genitalia.—Female.—The loose mesenchyma of the genital cord gives rise laterally to the *broad ligaments of the uterus* in females. A portion of the primitive genital fold unites the caudal end of the ovary to the genital cord. This acquires connective tissue and smooth muscle fibers and forms the *proper ligament of the ovary* (Fig. 233). Since the uterus develops in the genital cord, the ligament of the ovary extends to the posterior surface of the uterine wall. In the male the homologue of the proper ligament of the ovary is the *ligament of the testis*.

In both sexes the *inguinal fold* extends from the urogenital fold to the *inguinal crest*, located on the inside of the ventral abdominal wall, a point which marks the future entrance of the *inguinal canal*. The in-

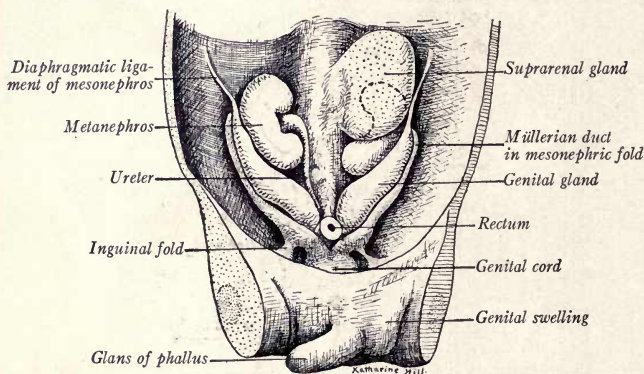


FIG. 232.—Ventral dissection of a human embryo of 23 mm., showing the urogenital organs. The right suprarenal gland has been removed to show the metanephros.

guinal fold thus forms a bridge in 14 mm. embryos between the urogenital fold, in the middle portion of which the uterus develops in the female, and the abdominal wall at the entrance of the inguinal canal (Fig. 232). In the inguinal crest is differentiated the conical anlage of the *chorda gubernaculi*, which later becomes a fibrous cord. The abdominal muscles develop around it, forming a tube, the *inguinal canal*, and the external oblique muscle leaves a foramen, through which the chorda connects with a second cord termed in the male the *ligamentum scroti*, in the female the *ligamentum labiale*. The chorda gubernaculi and the ligamentum labiale together constitute the *round ligament* of the uterus (Fig. 233), as they form a continuous cord extending from the urogenital fold to the base of the genital tubercle. With the development of the uterus in the urogenital fold, the round ligament becomes attached to its ventral surface.

Male.—The *ligamentum testis*, like the *ligamentum ovarii*, develops in the genital fold and extends from the caudal end of the testis to the mesonephric fold, at a point opposite the attachment of the inguinal fold. The inguinal fold, as we have seen, is continuous with the inguinal crest and the chorda gubernaculi. A cord develops in the mesonephric fold and connects the *ligamentum testis* with the chorda gubernaculi, for in the male the uterus does not intervene between these two. The chorda gubernaculi is continued to the integument of the scrotum by way of the *ligamentum scroti*. Thus there is formed a continuous cord, the *guber-*

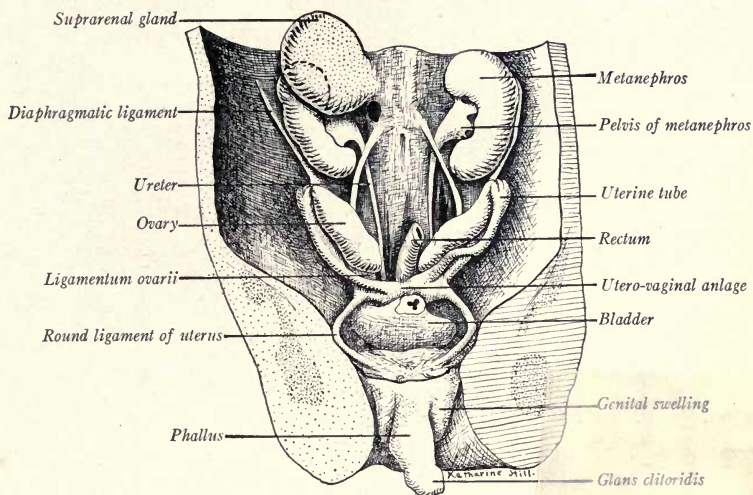


FIG. 233.—Ventral dissection of a female human embryo of 34 mm.. The urogenital organs are dissected out and the left suprarenal gland has been removed.

naculum testis, extending from the caudal end of the testis through the inguinal canal to the scrotal integument. The gubernaculum is composed of the *ligamentum testis*, a *mesonephric cord*, the *chorda gubernaculi*, and the *ligamentum scroti*. It is the homologue of the *ovarian ligament* plus the *round ligament of the uterus*, between which the uterus intervenes (Fig. 233.)

Descent of the Testis and Ovary.—The original position of the testis and ovary is changed during the later stages of development. At first they are elongate structures, extending in the abdominal cavity from the diaphragm caudally towards the pelvis (Fig. 220). Since their caudal ends continue to grow and enlarge while their cranial portions are atrophying, there is a wave-like shifting of the glands caudad. An actual internal descent, however, does not occur. When the process of growth and de-

generation is completed, the caudal ends of the testis lie at the boundary line between the abdomen and pelvis, whereas the ovaries are located in the pelvis itself, a position which they retain. Owing to the rotation of the ovary about its middle point as an axis, it takes up a transverse position. It also rotates nearly 180° about the Müllerian duct as an axis, and thus comes to lie caudal to the uterine tube.

The testis normally leaves the abdominal cavity and descends into the scrotum. As described above, there is early developed between the testis and the integument of the scrotum a fibrous cord, the *gubernaculum testis*. Owing to changes in the position of the ventral abdominal wall and umbilical arteries, changes connected with the return of the intestinal coils into the coelom, there are formed in each side of the abdominal wall sac-like pockets, the anlagen of the *vaginal sacs*. Close to each saccus (processus) vaginalis lies the caudal end of a testis, while extending into the scrotum outside the peritoneum is the gubernaculum testis. The *saccus vaginalis* later

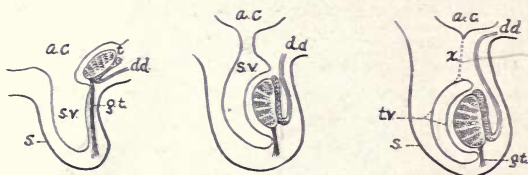


FIG. 234.—The descent of the testis; *a.c.*, Abdominal cavity; *d.d.*, ductus deferens; *g.t.*, gubernaculum testis; *s.*, scrotum; *sv.*, saccus vaginalis; *t.v.*, tunica vaginalis; *x.*, obliterated vaginal sac.

invaginates into the scrotum over the pubic bone. Due to the actual and relative shortening of the gubernaculum testis the descent of the testis into the vaginal sac begins during the seventh month of fetal life, and, by the end of the eighth month, or at least before birth, the testis is usually located in the scrotum (Fig. 234). It must be remembered that the testis and gubernaculum are covered by the peritoneum before the descent begins, consequently the testis follows the gubernaculum along the inguinal canal *dorsal to the peritoneum*, and, when it reaches the scrotum, is invaginated into the saccus vaginalis, but does not lie *in* the coelomic extension. The gubernaculum of a newborn is but one-fourth its length at the beginning of the descensus. After birth it atrophies almost completely.

Shortly after birth the narrow canal, connecting the saccus vaginalis with the abdominal cavity, becomes solid and its epithelium is resorbed. The vaginal sac, now isolated, becomes the *tunica vaginalis* of the testis. Its *visceral layer* is closely applied to the testis and its *parietal layer* forms the lining of the scrotal sac. The ductus deferens and the spermatic vessels and nerves are of course carried down into the scrotum with the testis and epididymis. They are surrounded by connective tissue, and,

with the spermatic vessels, constitute the *spermatic cord*. Owing to the descent of the testis, the ductus deferens is looped over the ureter in the abdomen (Fig. 238 C).

In the female, shallow peritoneal pockets, frequently persistent as the *diverticula of Nuck*, correspond to the vaginal sacs of the male. Rarely a more or less complete descent of the ovary into the labium majus occurs.

Anomalies.—At times, the testes remain undescended in the abdomen, a condition known as *cryptorchism* and associated with sterility in man. In some mammals (whale, elephant) it is the normal condition. The inguinal canals of man may remain open and allow the testes to slip back into the abdominal cavity. Such conditions lead to *inguinal hernia* of the intestine. Open inguinal canals, with a periodic descent during the breeding season, occur normally in some animals (rodents, bats).

C. THE EXTERNAL GENITALIA

Indifferent Stage.—The external genitalia of both sexes are similar until the beginning of the third month of development, when the indifferent anlagen become moulded into sexually distinct organs. There develops early in the midline of the ventral body wall, between the tail and umbilical cord, the *cloacal tubercle*. Upon this appears a knob-like structure, the *phallus*, and the two together constitute the *genital eminence* (Fig. 220). The cloacal tubercle forms about the base of the phallus *genital swellings*, more pronounced laterally. The phallus grows rapidly, carrying with it the phallic portion of the urogenital sinus (Fig. 219). At the end of the phallus the epithelium of the sinus forms a solid *urethral plate*.

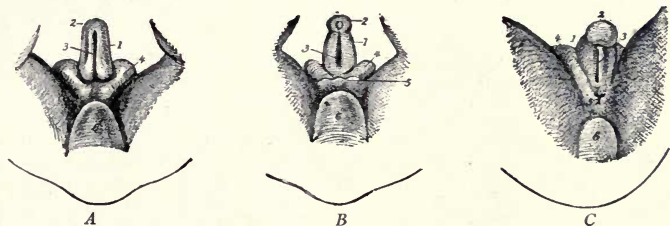


FIG. 235.—Three stages in the development of the external genitalia in human embryos of 24 to 34 mm. (after Tourneux in Heisler). Indifferent stage: 1, Phallus; 2, glans; 3, primitive urogenital opening; 4, genital tubercle or swelling; 5, anus; 6, coccyx.

Along the anal surfaces of the phallus, in the midline, the wall of the urogenital sinus breaks through to the exterior and forms the slit-like, primitive *urogenital opening* (Fig. 235). In embryos of 21 to 26 mm., at the end of the phallus, the glans is marked off from the base by a circular groove, the *coronary sulcus* (Figs. 232 and 235B).

Female.—A deep groove appears about the base of the phallus, separating it from the genital swellings, which become circular (Fig. 235 C). From the swelling differentiates: (1) cranially, the *mons pubis*; (2) laterally,

the right and left *labia majora*; (3) caudally, the *posterior commissure* (Fig. 236). The glans of the phallus forms the *glans clitoridis* of the female. On the anal surface of the phallus, beginning at the coronary sulcus, the primitive urogenital opening closes distally, forming the *urethral groove*. Proximally it remains open, as the definitive *urogenital opening* near the base of the phallus. The lips of this groove and opening enlarge and become the *labia minora*. The cranial surface of the phallus forms a fold,

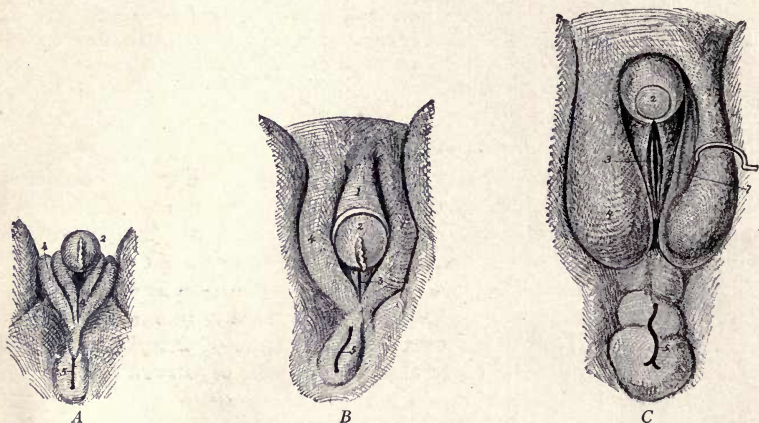


FIG. 236.—Three stages in the development of the female external genitalia (after Tournoux in Heisler). 1, Clitoris; 2, glans clitoridis; 3, urogenital aperture on each side of which are the labia minora (7); 4, labia majora; 5, anus; 7, labia minora.

the *prepuce*, which, however, is not the exact homologue of the male fore-skin. This in the female is represented by a ring-like rudiment at the base of the glans clitoridis (Felix, 1912).

Male.—The phallus grows rapidly at its base, so that the glans and primitive urogenital opening are carried some distance from the anus (Fig. 237). A cylindrical collar of the epithelium, incomplete on the anal side, grows down into the end of the glans, which becomes the *glans penis*. By the disappearance of the central cells of the epithelial downgrowth, an outer cylindrical mantle, the *prepuce*, or *fore-skin*, is formed about the spheroidal glans (cf. Fig. 158). Where the epithelial downgrowth is incomplete the glans and fore-skin remain connected, the persisting connection being the *frenulum prepuce*. The *corpora cavernosa penis* arise as paired mesenchymal columns. The *corpus cavernosum urethræ* results from the linking of similar, unpaired anlagen, one in the glans the other in the shaft.

The urogenital sinus, as we have seen, extends out into the phallus and in the glans becomes the solid urethral plate. With the great elonga-

tion of the male phallus, the open portion of the urogenital sinus also is lengthened and forms the greater part of the penile *urethra*. In fetuses of 70 mm. (C R), the groove-like primitive urogenital opening, located in the male near the glans and distant from the anus, begins to close and thus forms a further portion of the urethra. The lips of the urogenital opening, it will be remembered, correspond to the *labia minora*, or *nymphæ*, of the female. Finally, at 100 mm. (C H?), the solid urethral plate of the glans splits, forms a groove to the tip of the glans, and this groove in turn is closed, continuing the urethra to the definitive opening at the tip of the glans (Fig. 237 C). Owing to the rapid elongation of the penis, there is formed between its base and the anus an unpaired area, termed by Felix

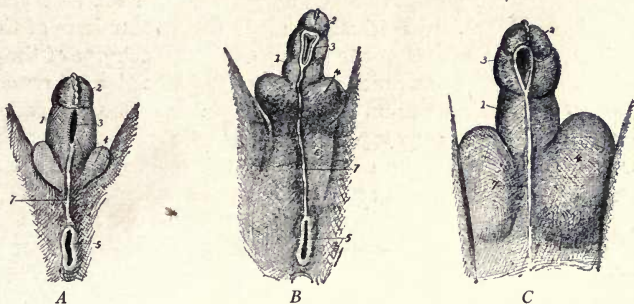


FIG. 237.—Three stages in the development of the male external genitals (after Tourneux in Heisler). 1, Penis; 2, glans; 3, urogenital groove; 4, genital swellings corresponding to labia majora of female; 5, anus; 7, scrotal area with perineo-scrotal raphe.

(1912) the the *scrotal area*, as it is the anlage of the scrotum (Fig. 237 A). At 60 mm. (C H) this forms a median scrotal swelling, continuous laterally with the paired genital swellings which form the labia majora in the female. When the scrotal sac develops in the scrotal area, the dense tissue in the median line is stretched and forms the *septum scroti*. The attachment of this septum forms an external median depression, the *raphe*. The testes descend into the vaginal sacs of the scrotum through the paired genital swellings, as described on p. 224, but the scrotum itself is an unpaired structure derived from the scrotal area. After the descent of the testes the genital swellings disappear (Fig. 237 C).

Comparing the male and female external genitalia, it is plain that the glans penis and glans clitoridis are homologous. The labia minora correspond to the phallic folds which close about the primitive urogenital opening on the anal surface of the penis. The greater part of the shaft of the male phallus does not develop in the female. On the other hand, the genital swellings enlarge and become the mons pubis and labia majora

of the female, while in the male they are only temporary structures. The scrotum does not develop in the female, being represented only by the posterior commissure of the labia majora.

Accessory Glands.—The *prostate gland* develops in both sexes as out-growths of the urethra, both above and below the entrance of the male ducts. The tubules arise at 55 mm. (C H) in five distinct groups and total an average number of 63 (Lowsley, 1912). The surrounding mesenchyme differentiates both white fibrous connective tissue and smooth muscle fibers into which the anlagen of the prostate grow. In the female the homologue is rudimentary; these isolated *paraurethral ducts* (of Skene) number at most three.

The *bulbo-urethral glands* (of Cowper) arise in male embryos of 30 mm. (C R) as solid, paired epithelial buds from the entoderm of the urogenital sinus. The buds penetrate through the mesenchyme of the corpus cavernosum urethræ, about which they enlarge. The glands branch, and, at 120 mm. (C R), the epithelium becomes glandular. The *vestibular glands* (of Bartholin) are the homologues in the female of the bulbo-urethral glands. They appear at the same age as the male glands, grow until after puberty, and degenerate after the climacterium.

HOMOLOGIES OF INTERNAL AND EXTERNAL GENITALIA

<i>Male</i>	<i>Indifferent Stage</i>	<i>Female</i>
Ductuli efferentes. Paradidymis.	Mesonephric collecting tubules. Cranial group. Caudal group.	Epoöphoron. Paraöphoron.
Ductus epididymidis. Ductus deferens. Seminal vesicle. Ejaculatory duct.	Mesonephric duct.	Gartner's duct.
(1) Appendix testis. (2) (3) Utriculus prostaticus (Vagina masculina).	Müllerian duct.	(1) Uterine tube. (2) Uterus. (3) Vagina.
Colliculus seminalis.	Müller's tubercle.	Hymen.
(1) Prostatic and membranous urethra. (2) Prostate gland. (3) Bulbo-urethral glands.	Urogenital sinus.	(1) Urethra and vestibule. (2) Paraurethral ducts. (3) Vestibular glands.
Glans penis. Anal surface of penis. (1) (2) (3) Scrotum.	Phallus. Glans. Lips of urethral groove. Genital swellings.	Glans clitoridis. Labia minora. (1) Mons pubis. (2) Labia majora. (3) Posterior commissure.

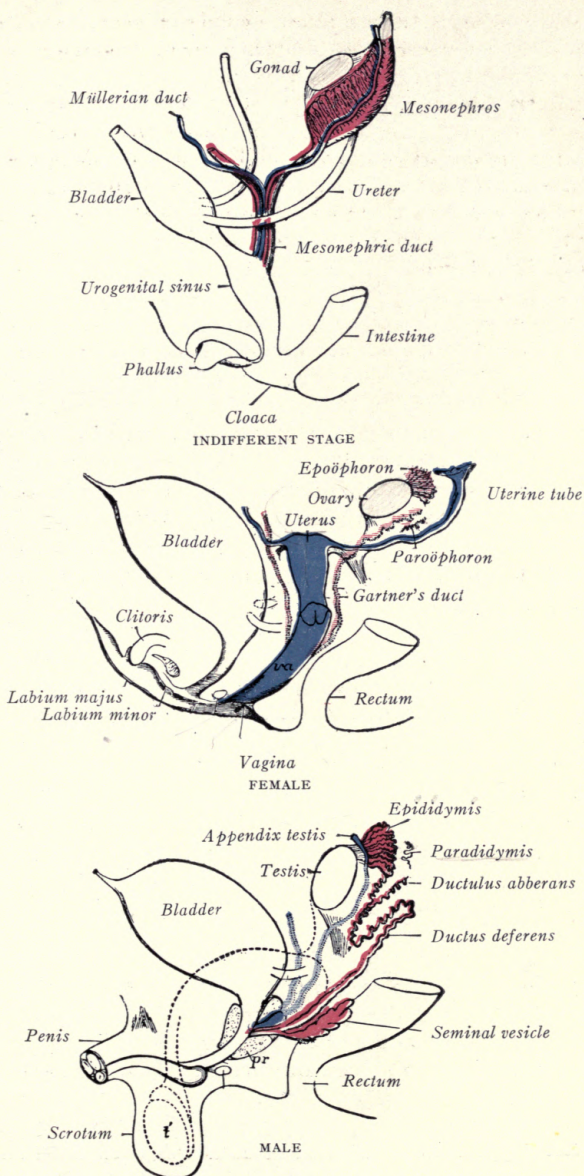


FIG. 238.—Diagrams to show the development of male and female genital organs from a common type (after Allen Thompson).

Anomalies.—If the lips of the slit-like urogenital opening on the under surface of the penis fail to fuse, *hypospadias* results. Rarely there is a similar defect on the upper surface—*epispadias*.

True hermaphroditism consists in the presence of both testes and ovaries in the same individual. It is of rare occurrence in birds and mammals, is not uncommon in the lower vertebrates, and is the normal condition in many invertebrates (worms, molluscs). According to Pick (1914), there are only four authentic cases in man; these have on one side, at least, a combined ovotestis. The internal genitalia are faultily bisexual. The external genitalia show mixed male and female characteristics. The secondary sexual characters (beard, mammæ, voice, etc.) are usually intermediate, tending now one way, now the other.

False hermaphroditism is characterized by the presence of the genital glands of one sex in an individual whose secondary sexual characters and external or internal genitalia resembles those of the opposite sex. In masculine hermaphroditism an individual possesses testes, often undescended, but the external genitals (by retarded development) and secondary characters are like those of the female. In feminine hermaphroditism ovaries are present, and sometimes descended, but the other sexual characters, such as enlarged clitoris or fused labiæ, simulate the male. The cause of hermaphroditism is unknown.

THE UTERUS DURING MENSTRUATION AND PREGNANCY: PLACENTA AND DECIDUAL MEMBRANES

Two sets of important changes take place normally in the wall of the uterus. One of these is periodic between puberty and the menopause (about the forty-fifth year) and is the cause of *menstruation* (monthly flow). These periodic changes, comparable to the œstrus cycle in lower animals, may also be regarded as preparatory to the second set of changes which take place if pregnancy occurs and give rise to the decidual membranes and placenta.

Menstruation.—The periodic changes that accompany the phenomenon of menstruation form a cycle which occupies twenty-eight days. This period is divided into: (1) a phase of uterine congestion—six or seven days; (2) a phase of hemorrhage and epithelial desquamation—three to five days; (3) a phase of regeneration of the uterine mucosa—four to six days; (4) finally, an interval of rest or slight regeneration—twelve to sixteen days.

During the first phase, the uterine mucosa is thickened to two or three times its resting condition, both because of vascular congestion and on account of the actual increase of connective tissue cells. The uterine glands become longer, and their deeper portions especially are dilated and more convoluted because they are filled with secretion. Blood escapes from the enlarged capillaries by diapedesis and forms subepithelial masses. At the end of this stage, the uterine mucosa shows a deep spongy layer and a superficial compact layer, these corresponding to similar layers in the decidual membranes of pregnancy.

During the second phase, that of menstruation proper, the superficial blood vessels rupture and add to the blood escaping into the uterine cavity;

there is also an active discharge of secretion from the uterine glands. The surface epithelium and a portion of the underlying tissue may or may not be desquamated. In some cases the surface epithelium and most of the compact layer may be expelled, aided by painful contractions of the uterus.

In the third stage, the mucosa becomes thin, with straight, narrow glands, between which are fusiform, closely packed stroma cells. Any surface epithelium which has been desquamated is regenerated from the epithelium of the glands, and gradually the mucosa returns to a resting condition, during which, however, there is a slow process of cell proliferation.

Implantation of the Ovum.—The earliest known human ova are already completely embedded in the uterine mucosa. From the careful study of early human embryos by Bryce and Teacher, Peters, Herzog, and others, and from more complete observations on other mammals, such as the guinea pig, the course of events in man is reasonably certain.

Ovulation sets the ripe ovum free within the abdominal cavity, from whence the beating cilia on the fimbriæ of the uterine tube sweep it into the tubal ampulla. There it may be fertilized and carried to the uterus by the cilia of the tubal epithelium. During this period of migration, which is estimated as occupying about eight days, the ovum loses its surrounding follicle cells and pellucid membrane and begins its development. Thus when it reaches the uterus, and is ready for implantation, it is an embryo with trophoctoderm developed, although the blastodermic vesicle is not more than 0.2 mm. in diameter (von Skee).

Since ovulation occurs most often in the intermenstruum, Grosser believes that the embryo reaches the uterus during the premenstrual period. The congestion and loosening of the uterine tissue at this time would seemingly favor the implantation of the embryo, and the glandular secretion might afford nutriment for its growth until implantation occurs. The first phase of menstruation, according to this view, prepares the uterine mucosa for the reception of the embryo. If pregnancy supervenes, it soon inhibits any further premenstrual changes so that menstruation does not occur. Menstruation proper would then represent an over-ripe condition of the mucosa and the abortion of an unfertilized ovum.

If the ovum becomes implanted and develops elsewhere than in the uterus the condition is known as an *extrauterine*, or *ectopic pregnancy*. The commonest site is the uterine tube, *tubal pregnancy*. Attachment to the peritoneum, *abdominal pregnancy*, and the development of an unexpelled ovum within the ruptured follicle, *ovarian pregnancy*, are known also.

The embryo penetrates the uterine mucosa as would a parasite, the trophoctoderm supposedly producing an enzyme which digests away the maternal tissues until the embryo is entirely embedded (Fig. 239). During implantation, the trophoctoderm also absorbs nutriment (chiefly blood) from the uterine mucosa for the use of the embryo. The process of im-

plantation is supposed to occupy one day. At the point where the embryo enters the mucosa a fibrin clot soon appears and eventually the opening is completely closed (Fig. 239).

The Decidual Membranes (Figs. 240 and 241).—With the increase in size of the embryo and chorionic vesicle, the superficial covering layer of the maternal mucosa bulges into the cavity of the uterus and forms the *decidua capsularis* (old term, decidua reflexa). The deep layer of the mucosa next the inner side of the embryo forms the anlage of the future maternal placenta and is the *decidua basalis* (decidua serotina). The mucosa lining

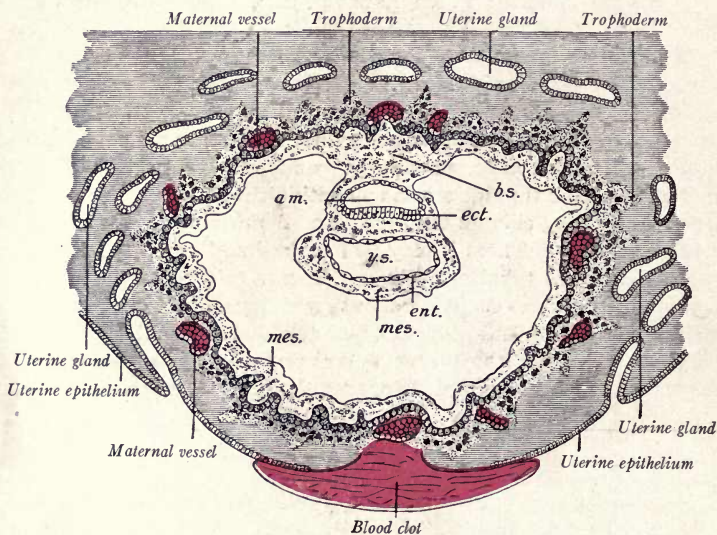


FIG. 239.—Section through a human embryo of .16 mm. embedded in the uterine mucosa (semi-diagrammatic after Peters). *am.*, Amniotic cavity; *b.s.*, body stalk; *ect.*, ectoderm of embryo; *ent.*, entoderm; *mes.*, mesoderm; *y.s.*, yolk sac.

the rest of the uterus is differentiated into the *decidua vera* (decidua parietalis of Bonnet).

Differentiation of the Trophoblast.—The chorion is at first composed of an inner, mesodermal layer and an outer, epithelial layer, the *trophoblast* (Fig. 74). From the trophoblast there is developed an outer syncytial layer, the *trophoderm* (Fig. 239). This invades and destroys the maternal tissues. In the latter large vacuoles are formed, either directly by the syncytial tissue (Bryce and Teacher), or by the blood escaping from the ruptured vessels under pressure (Peters), and thus *blood lacunæ* are produced. The trophoderm thickens at intervals and

forms on the surface of the chorion solid cords of cells, the *primary villi* (Fig. 239). The chorionic mesoderm grows out into these cords, which branch profusely and become *secondary*, or *true villi* (Fig. 242). During the development of the villi, the blood lacunæ in the trophoderm around the villi expand, run together, and produce *intervillous blood spaces* which surround the villi and bathe the epithelium with blood. The syncytial trophoderm, from being a spongy network, is now reduced to a continuous

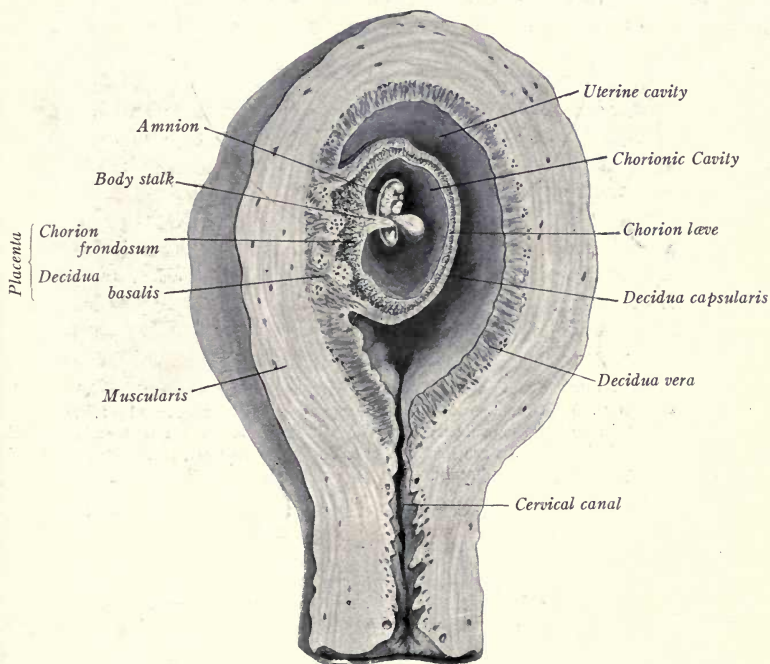


FIG. 240.—Gravid uterus of about one month, longitudinal section.

layer covering the outer surfaces of the villi and chorion. Branches of the umbilical vessels develop in the mesoderm of the chorion and villi. The mesodermal core of each villus and its branches is now covered by a two-layered epithelium, an inner, ectodermal layer with distinctly outlined cuboidal cells, and an outer, syncytial trophoderm layer (Fig. 248 A). The epithelium also forms solid *columns* of cells which anchor the ends of certain villi to the maternal tissue. Islands, or nodes, of epithelial cells, are attached to the villi or lie free in the decidua basalis; they represent

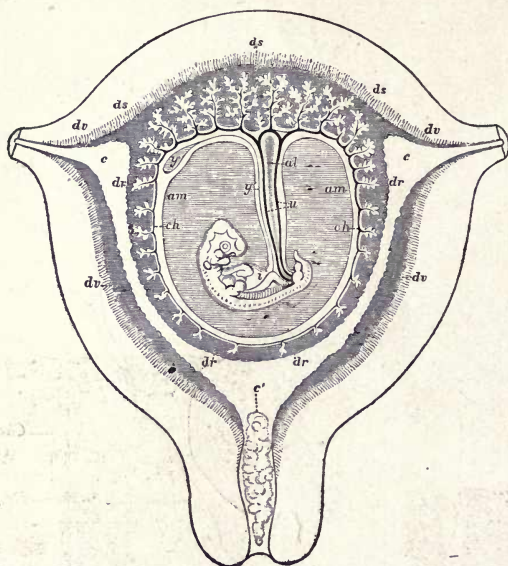


FIG. 241.—Diagrammatic section through a pregnant uterus at the seventh or eighth week (after Allen Thomson). *c, c*, Openings of uterine tubes; *c'*, cervix with mucous plug; *dv*, decidua vera or parietalis; *dr*, decidua capsularis; *ds*, decidua basalis; *ch*, chorion with villi; the villi extending into the decidua basalis are from the chorion frondosum; *am*, amnion; *u*, umbilical cord; *al, al*, allantois; *y, y'*, yolk sac and stalk.

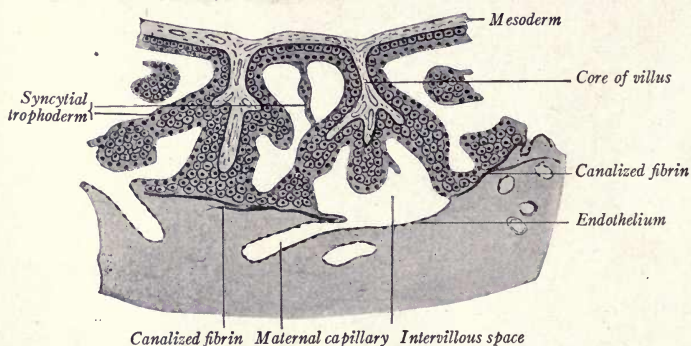


FIG. 242.—Diagram illustrating the development of the chorionic villi and placenta (after Peters).

portions of the primitive trophoderm. In the vessels of the chorionic villi the chorionic circulation of the embryo is established. The blood vessels of the uterus open into the intervillous blood spaces and here the maternal blood circulates. The syncytial trophoderm covering the villi is bathed in the maternal blood. Its functions are three-fold: (1) like endothelium it prevents the coagulation of the maternal blood; (2) it allows transudation between the blood of fetus and mother; and (3) it assimilates substances from the maternal blood and transfers them to that of the embryo. According to Mall (1915), the trophoderm also forms a wall which dams or plugs the blood vessels as soon as eroded, and, with the decidua (p. 240), permits but little blood to pass into the intervillous spaces (cf. p. 241).



A



B

FIG. 243.—Human ova: A, of three weeks; B, of six weeks, showing formation of the chorion l  ve by degeneration of the chorionic villi (De Lee).

The Chorion L  ve and Frondosum.—The villi at first cover the entire surface of the chorion. As the embryo grows more and more out into the uterine cavity, the decidua capsularis and that portion of the chorion attached to it are compressed, and the circulation in the intervillous spaces of these structures is cut off (Figs. 241 and 243). Thus, beginning at the pole of the decidua capsularis, the villi in this portion of the chorion degenerate during the fourth week and form the *chorion l  ve*. The villi on that part of the chorion which is attached to the decidua basalis continue their development, and, persisting, form the *chorion frondosum*. This, with the decidua basalis of the uterus, constitutes the *placenta* (Fig. 240). The embryo is attached first to the chorion frondosum by the body stalk (Figs. 77 B and 239), later by the umbilical cord (Fig.

241). Through the umbilical vein and arteries in the cord the placental circulation of the embryo takes place.

The Decidua Vera.—During the first phase of menstruation the uterine mucosa begins to differentiate into a broad, superficial *compact layer* and into a narrower, deep *spongy layer* in which are found the dilated ends of the uterine glands. After pregnancy these two layers are still further differentiated in the wall of the *decidua vera* and *decidua basalis*. The *compact layer* is much thicker than the spongy layer and in it are found numerous stroma cells, enlarged blood vessels, and *decidual cells* (Fig. 244). The decidual cells, frequently multinucleate, are derived

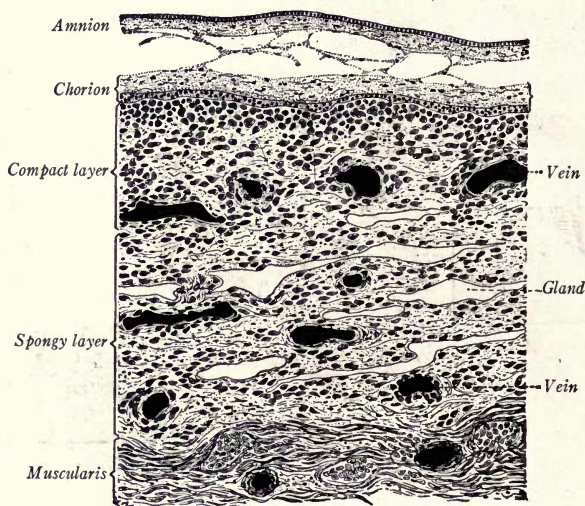


FIG. 244.—Vertical section through the wall of the uterus about seven months pregnant, with the membranes *in situ* (Schaper in Lewis and Stöhr). $\times 30$.

from the stroma cells of the mucosa. They are large, being $50\ \mu$ in diameter, with clear cytoplasm and vesicular nuclei. Their function is in doubt. Glycogen has been found in them, but during the later months of pregnancy many of them degenerate.

In the *spongy layer* of the mucosa occur the enlarged and tortuous *uterine glands of pregnancy* (Fig. 244). During the first two months of pregnancy the long axes of the glands are perpendicular to the surface of the mucosa. Later, as the decidua is stretched and compressed owing to the growth of the fetus, the glands are broadened and shortened and the cavities of the glands become elongated clefts parallel to each other and to the surface of the decidua. The gland cells become stretched

and flattened until they resemble endothelial cells. At birth, or in case of late abortion, the plane of separation is in the spongy layer. Only the deep portions of the glands remain attached to the uterine wall, and, by the division of their cells, regenerate the epithelium of the uterus.

The Decidua Capsularis.—The capsularis, as we have seen, becomes thin as the embryo grows (Fig. 241). To it is attached the *chorion laeve*, the villi of which degenerate. During the fourth month the increased size of the fetus brings the capsularis into contact with the decidua vera with which it fuses, thereby obliterating the uterine cavity. Eventually it largely degenerates, completely so opposite the internal os uteri, where the chorionic villi are obliterated also. During pregnancy, the lumen of the cervix is closed by a plug formed by the secretions of the glands opening into the cervix uteri (Fig. 241).

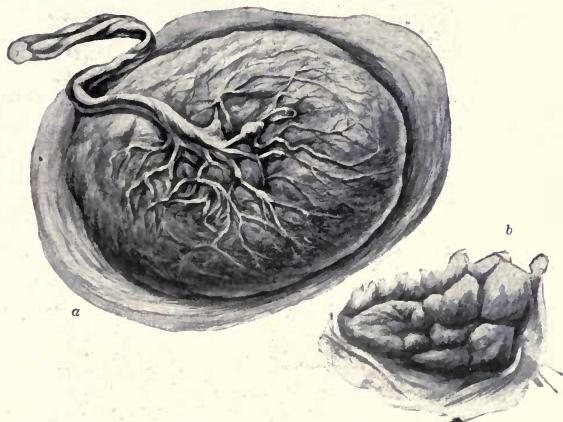


FIG. 245.—Mature placenta. *a*, Entire organ, showing fetal surface with membranes attached to the periphery; *b*, a portion of attached surface showing cotyledons (Heisler).

The Placenta.—The placenta is composed of the *decidua basalis*, fetal constituting the maternal portion, and of the *chorion frondosum*, the contribution (Fig. 240). The area throughout which the villi of the chorion frondosum remain attached to the decidua basalis is somewhat circular in form, so that at term the placenta is disc-shaped, about seven inches in diameter and one inch thick (Fig. 245). Near the middle of its fetal surface is attached the umbilical cord, and this surface is formed by the amnion, the mesoderm of which is closely applied to, and fused with, that of the chorion frondosum (Fig. 246).

The Chorion Frondosum.—The villi of this portion of the chorion form profusely branched, tree-like structures which lie in the intervillous

spaces (Fig. 247). The ends of some of the villi are attached to the wall of the decidua basalis and are known as the *anchoring villi*. In the connective-tissue core of each villus are commonly two arteries and two veins

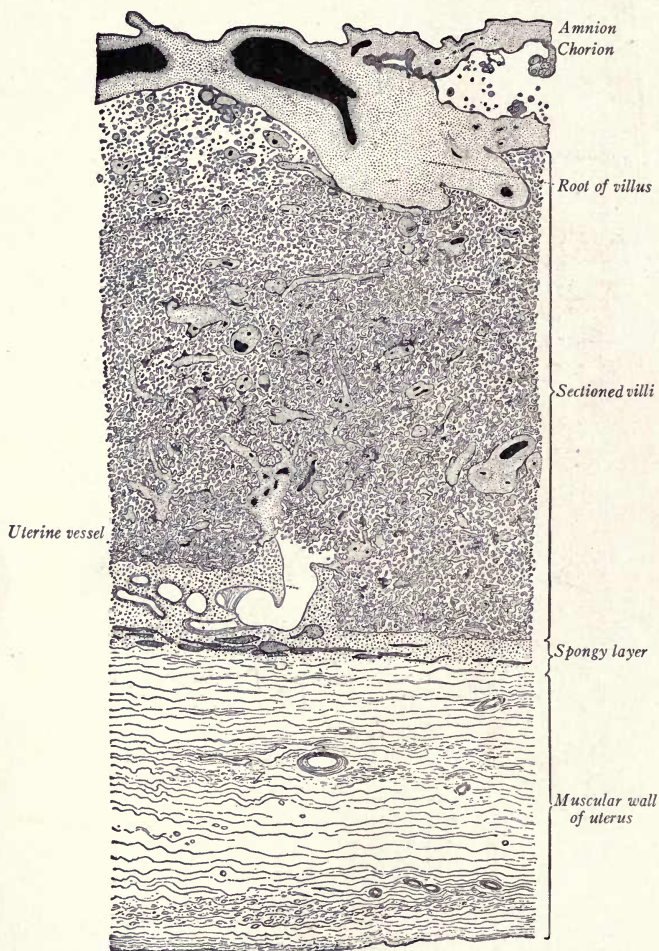


FIG. 246.—Section through a normal placenta of seven months *in situ* (Minot). $\times 5$.

(branches of the umbilical vessels), cells like lymphocytes, and special cells of Hofbauer, apparently undergoing degeneration. Lymphatics are also present. The epithelium of the villi, as we have seen, is at first

composed of a layer of trophoctoderm with the outlines of its cuboidal cells sharply defined (Fig. 248 A). This layer (of Langhans) forms and is covered by a syncytium, the trophoderm. In the later months of pregnancy, as the villi grow, the trophoctoderm is used up in forming the syncytium, so that at term the trophoderm is the only continuous epithelial layer of the villi (Fig. 248 B). About the margin of the placenta the trophoctoderm persists as the *closing ring*, which it continuous with the epithelium of the chorion laeve.

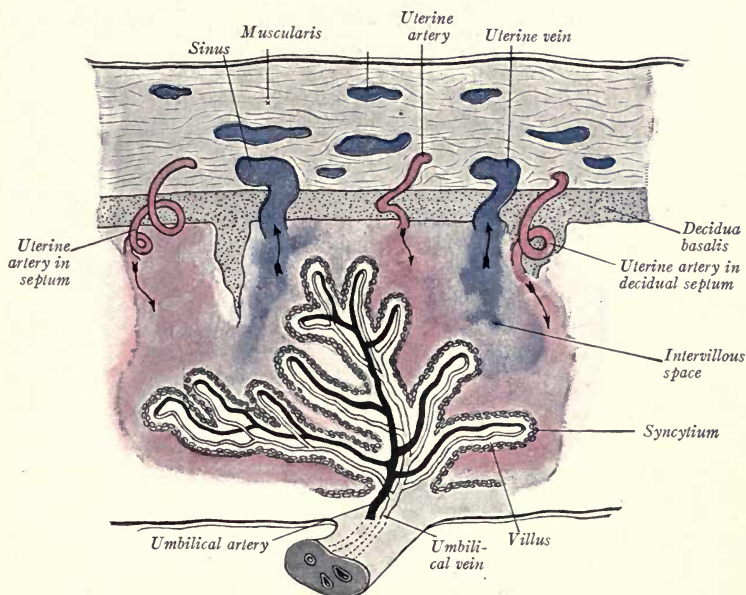


FIG. 247.—Scheme of placental circulation (Kollmann). Arrows indicate supply and exhaust of blood in the intervillous spaces.

The Decidua Basalis.—This, the maternal placenta, like the decidua vera is differentiated into a *compact layer*, or *basal plate*, which forms the floor of the intervillous spaces, and into a deep spongy layer (Figs. 246 and 247). The first is the remains of the *compact layer* of the uterine mucosa, formed during the premenstrual phase and partially destroyed by the implantation of the ovum. The second is the modified *spongy layer* of the premenstrual period, and, though thinner, shows the same differentiation as in the decidua vera. The glandular spaces are less numerous in the spongy layer of the decidua basalis; between the spaces

occur syncytial giant cells to be derived from the trophoderm of the villi. It is in the plane of this spongy layer that the separation of the placenta takes place at birth. The decidua is said to prevent excessive hæmorrhage during the earlier part of pregnancy by acting as a dam between the chorionic villi and the eroded uterus (cf. p. 235).

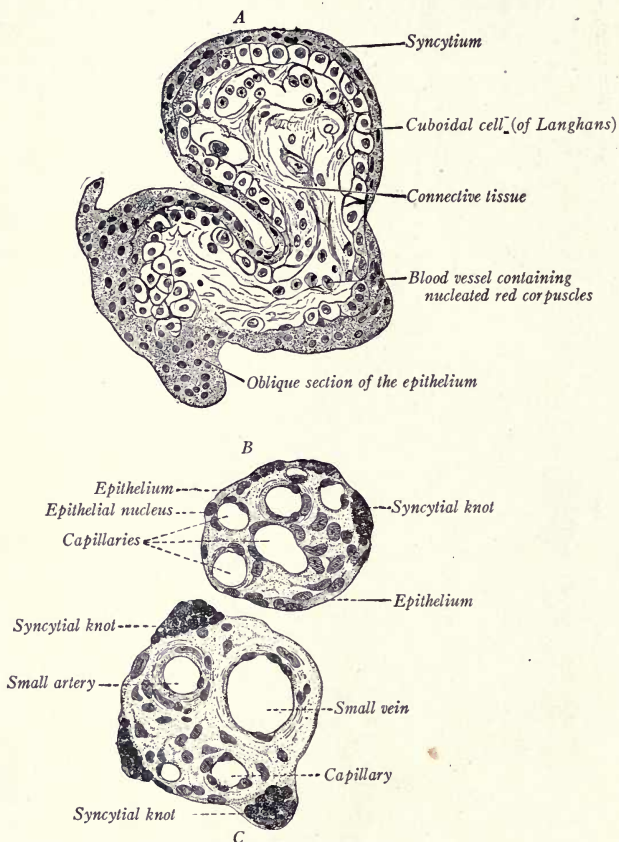
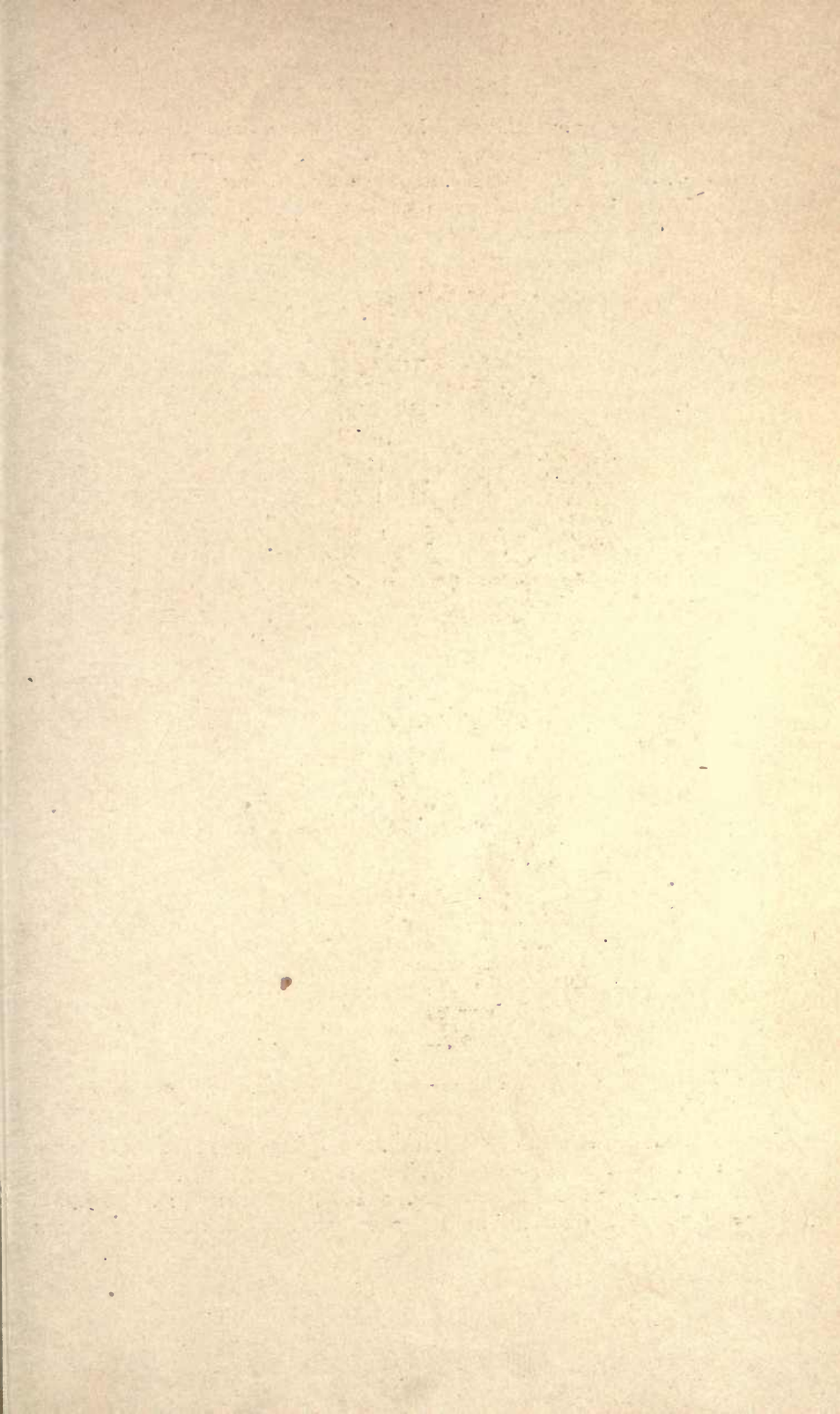


FIG. 248.—Transverse sections of chorionic villi: *A*, at the fourth week; *B*, *C*, at the end of pregnancy (Schaper in Lewis and Stöhr).

The *basal plate*, or *compact layer* of the decidua basalis, is composed of a connective-tissue stroma containing decidual cells, canalized fibrin, and persisting portions of the epithelium of the villi. The 'canalized fibrin' (Fig. 242) forms chiefly by a fibrinoid necrosis of the mucosa, but



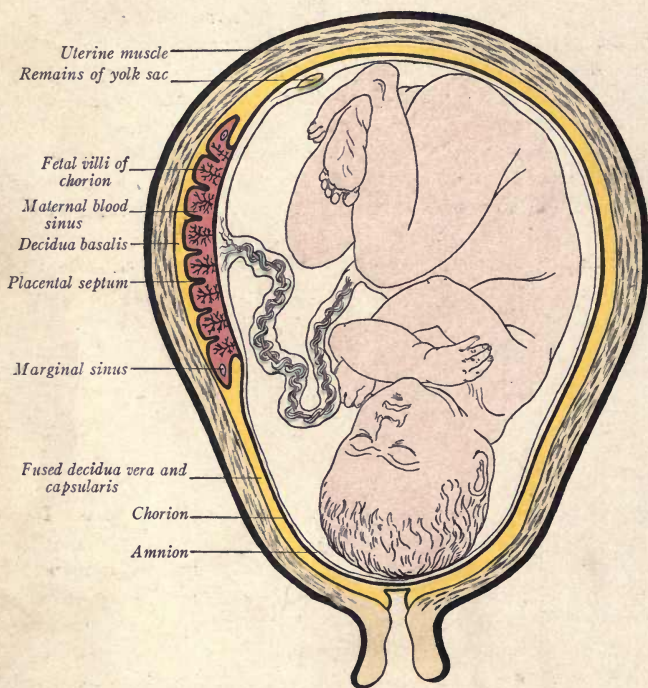


FIG. 249.—Section of the uterus, showing the relation of an advanced fetus to the placenta and membranes (Ahlfeld).

the fibrin of the maternal blood and the chorionic trophoderm also participate (Mall, 1915). From the basal plate, septa extend into the intervillous spaces but do not unite with the chorion frondosum (Grosser). Near term, these constitute the *septa placenta* which incompletely divided the placenta into lobules, or *cotyledons* (Figs. 245 and 247). The maternal arteries and veins pass through the basal plate, taking a sinuous course and opening into the intervillous spaces (Fig. 247). Near their entrance they course obliquely and lose all but their endothelial layers. The original openings of the vessels into the intervillous spaces were formed during the implantation of the ovum, when their walls were eroded by the invading trophoderm of the villi. As the placenta increases in size, the vessels grow larger. The ends of the villi are frequently sucked into the veins and interfere with the placental circulation. At the periphery of the placenta is an enlarged intervillous space that varies in extent but never circumscribes the placenta completely. This space is the *marginal sinus* through which blood is carried away from the placenta by the maternal veins (Fig. 249). The blood of the mother and fetus does not mix, although the epithelial cells of the villi are instrumental in transferring nutritive substances to the blood of the fetus and in eliminating wastes from the fetal circulation into the maternal blood stream of the intervillous spaces.

Mall (1915) states that there is little evidence of an actual intervillous circulation; the decidua and trophoderm are active in preventing this (pp. 239 and 240). Some embryologists hold that the intervillous circulation is peculiar to the second half of pregnancy. In summary, Mall regards the entire question as still open.

Relation of the Fetus to the Placenta and the Separation of the Decidual Membranes at Birth.—The relation of the embryo to the fetal membranes has been described on p. 73 *f.f.* During the first months of pregnancy the embryo floats in the cavity of the amnion, attached to the placenta by the umbilical cord (Fig. 241). Later, as we have seen, the amnion fuses more or less completely to the chorion frondosum and laeve. The decidua capsularis fuses with the decidua vera and largely disappears. Before birth, the placenta is concave on its amniotic surface, its curvature corresponding to that of the uterus (Fig. 249). At term, the duration of which is taken as ten lunar months, the muscular contractions of the uterus, termed 'pains,' bring about a dilation of the cervix uteri, the rupture of the amnion and chorion laeve, and cause the extrusion of the child. With the rupture of the membranes the amniotic liquor is expelled, the fetal membranes remaining attached to the decidual membranes. The pains of labor begin the detachment of the decidual membranes, the plane of their separation lying in the spongy layer of the decidua basalis and

decidua vera, where there are only thin-walled partitions between the enlarged glands (Fig. 246). Following the birth of the child, the tension of the umbilical cord and the 'after pains' which diminish the size of the uterus, normally complete the separation of the decidual membranes from the wall of the uterus. The uterine contractions serve also to diminish the size of the ruptured placental vessels and prevent extensive hemorrhage. From the persisting portions of the spongy layer and from the epithelium of the glands, the tunica propria, glands, and epithelium of the uterine mucosa are regenerated.

The decidual membranes, and the structures attached to them when expelled, constitute the 'after birth.' The placenta usually is everted so that its amniotic surface is convex, its maternal surface concave. It is composed of the amnion, chorion frondosum, chorionic villi with intervillous spaces incompletely divided by the septa into cotyledons, and includes on the maternal side the basal plate and a portion of the spongy layer of the decidua basalis. Near the center of the placenta is attached the umbilical cord, and at its margins the placenta is continuous with the decidua vera and the remains of the chorion laeve and decidua capsularis.

Placentation.—Except the egg-laying monotremes, all mammals form some kind of placenta. In the simplest type (Ungulates) the chorionic villi fit into crypts of the uterine mucosa; as the two surfaces are merely apposed, the endometrium is not cast off at birth. The highest type, as in Rodentia and Primates, is characterized by a partial destruction of the uterine mucosa, so that the chorionic villi, dangling in cavernous spaces, are bathed by the maternal blood which issues from eroded vessels; due to intimate fusions, the mucosa is largely lost at birth. Intermediate conditions are found in the Carnivora; in this group there is a chorionic invasion and erosion of the endometrium, yet the maternal blood circulates within intact vessels.

Position of the Placenta in Utero and its Variations.—The position of the placenta is determined by the point at which the embryo is implanted. In most cases it is situated on either the dorsal or ventral wall of the uterus. Occasionally it is lateral in position, and, very rarely (1 in 1600 cases), it is located near the cervix and covers the internal os uteri, constituting a *placenta prævia*. A partially or wholly duplicated placenta, or accessory (*succenturiate*) placentas may be formed from persistent patches of villi on the chorion laeve. Cases have been observed in which from three to seven subdivisions of the placenta occurred.

Gross Changes in the Uterus.—During pregnancy the uterus enlarges enormously, due chiefly to the hypertrophy of its muscle fibers, and the fundus reaches the level of the xiphoid process. After birth, it undergoes rapid involution; at the end of one week it has lost one-half its weight, and in the eighth week the return is complete. The mucosa is regenerated in two or three weeks from the remains of the spongy layer (Fig. 246).

CHAPTER IX

THE DEVELOPMENT OF THE VASCULAR SYSTEM

THE PRIMITIVE BLOOD VESSELS AND BLOOD CELLS

BOTH the blood cells and the primitive blood vessels arise from a tissue termed by His the *angioblast*. Its origin has long been in doubt but recent investigations by Maximow, Felix, Schulte, and Bremer point to the mesoderm.

In the body stalk of very young human embryos, Bremer (1914) has shown the direct origin of angioblast from splanchnic mesothelium. Moreover since this angioblast may antedate that of the yolk sac an entodermal origin is excluded. According to Minot (1912), Rückert, and others, the angioblast arises in the wall of the yolk sac from the entoderm. A further view, favored by Hertwig (1915), derives the blood cells from entoderm, the vascular endothelium from mesoderm.

The angioblast consists initially of isolated, solid cords and masses of cells which appear first in the splanchnic mesoderm of the body stalk and yolk sac. The solid cords of angioblast soon hollow out, the peripheral cells forming the *endothelium of the primitive vessels*, the inner cells, bathed by a clear fluid, persisting as the *primitive blood cells*, or mesamœboids of Minot. By the union of the isolated vascular spaces, the cellular network is soon converted into a vascular plexus which completely covers the human yolk sac. In the wall of the yolk sac this network is termed the *area vaculosa*, and here aggregations of blood cells form the *blood islands* (Figs. 33 and 79).

HÆMOPOIESIS

Two sharply contrasted views are held as to the mode of origin (*hæmopoiesis*) of the various adult blood elements. According to the *monophyletic theory*, a common stem-, or mother cell, such as the mesamœboid, gives rise to all types of blood elements, both red and white. The *polyphyletic theory*, on the contrary, asserts that the erythroplastids and the several kinds of white cells are derived from two or more distinct mother cells. The total evidence seems to favor the monophyletic view, yet there are able dissenters (Stockard, 1915).

The Primitive Blood Cells or Mesamœboids.—These show large, vesicular nuclei surrounded by a small amount of finely granular cytoplasm (Fig. 250 a). They are without a distinct cell membrane and are assumed

to be amœboid. During embryonic life, the mesamœboid cells multiply rapidly by mitosis and develop successively in the wall of the yolk sac, in the young blood vessels, and in the liver, lymphoid organs, and red bone marrow.

Besides the mesamœboids of extra-embryonic origin, totipotent blood-forming cells appear to rise both from the mesoderm of the embryo and from the mesenchymal cells of adult connective tissue; such cells are believed by Maximow (1906; 1908) to produce all types of blood elements.

Origin of the Erythrocytes.—The red blood corpuscles take their origin as *erythroblasts* from the mesamœboid cells of the embryo, and from the *premyelocytes* of adult connective tissue and bone marrow.

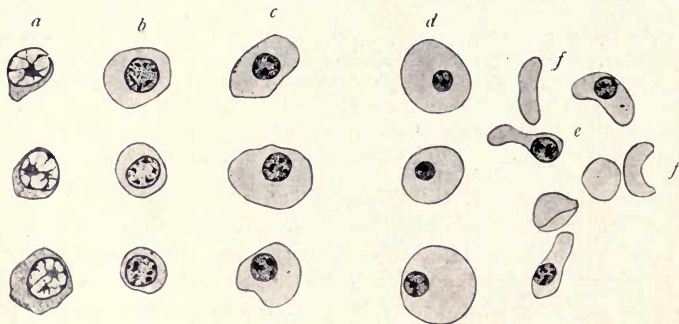


FIG. 250.—Blood cells from human embryos of 12 and 20 mm. $\times 1160$. *a*, Primitive mesamœboid cells; *b*, erythroblasts; *c*, *d*, *e*, normoblasts; *f*, erythrocytes. (*a*–*c*, from 12 mm., *d*–*f*, from 20 mm. embryo.)

1. *Erythroblasts* (ichthyoid blood cells of Minot, so-called because they resemble the typical red blood cells of fishes,) are characterized by the presence of hæmoglobin in the homogeneous cytoplasm, which is thus colored red. The nuclei are vesicular, with granular chromatin (Fig. 250 *b*). There is a definite cell membrane. For the first six weeks of development (12 mm.) the erythroblast is the only red blood cell found.

2. *Normoblasts*, also termed sauroid blood cells because they resemble the red blood cells of adult reptiles, are first formed in the liver from the erythroblasts, and are predominant in embryos of two months. They are distinguished by their small, round nuclei with dense chromatin which stains so heavily that little or no structure can be seen (Fig. 250 *c*, *d*). The cytoplasm is larger in amount than in erythroblasts.

3. *Erythrocytes* (red blood corpuscles, erythroplastids) are developed in mammals from normoblasts which lose their nuclei by extrusion (Fig.

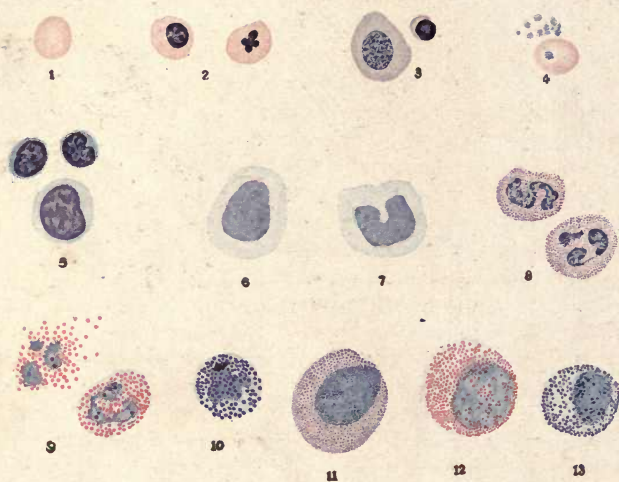


FIG. 252.—Human blood-cells (Todd). $\times 1000$. 1, Erythroplastid; 2, normoblasts; 3, erythroblast and normoblast; 4, blood-plates, one lying on a red corpuscle; 5, lymphocytes, large and small; 6, 7, large mononuclear leucocytes, polar and profile views; 8, neutrophilic leucocytes; 9, eosinophilic leucocytes; 10, basophilic leucocyte; 11, neutrophilic myelocyte; 12, eosinophilic megalocyte; 13, basophilic myelocyte.

250 f). The nucleus, extruded as several small granules or as a whole (Fig. 251), is ingested by phagocytes.

Emmel (1914), studying cultures of blood cells from pig embryos, has observed the formation of bodies resembling erythrocytes by a process of cytoplasmic constriction. He suggests that this may be their normal method of development in the embryo.

The first red blood corpuscles are spherical and are formed during the second month, chiefly in the liver. During the third month the enucleated erythrocytes predominate (Fig. 250 f). Although usually cup-like in preserved material, their normal shape is that of a biconcave disc (Arey, 1917). During the later months of fetal life, the red blood corpuscles are developed in the liver, in the red bone marrow, and probably in the spleen. According to the view of Minot, the cells from which they take their origin are mesamœboids which have lodged in the blood-forming organs and undergo cell division and differentiation there. In the bone marrow these cells are known as *premyelocytes*. They differentiate into both *erythroblasts* and *myelocytes*; from the former normoblasts and erythrocytes arise, from the myelocytes the granular leucocytes are developed. Soon after birth the red bone marrow is the only source of new red blood corpuscles.

Origin of the Leucocytes.—The white blood cells are divided into non-granular and granular types (Fig. 252). According to the monophyletic view, it is assumed that both types are derived from the primitive mesamœboid cells of the embryo.

I. Non-granular Leucocytes:

1. *Lymphocytes* are ordinarily about the size of a red corpuscle but some are twice as large. They constitute from 22 to 25 per cent of the leucocytes in adult blood and are developed in the lymphoid organs of the embryo and adult. The spherical nucleus, containing numerous small masses of chromatin, stains darkly and is surrounded by a narrow zone of clear, faintly basophilic cytoplasm.

2. *Large mononuclear leucocytes* are two or three times the size of a red corpuscle. They possess a clear nucleus, usually indented, and considerable faintly basophilic cytoplasm. They comprise 1 to 3 per cent of all leucocytes and are developed from the endothelial or reticular cells of lymph glands (Evans, 1914; Kyes, 1915).

II. Granular or Polymorphonuclear Leucocytes:

The blood-forming cells lodged in the red bone marrow are known as

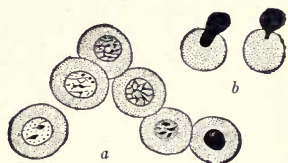


FIG. 251.—The development of red corpuscles in cat embryos (Howell). *a*, Successive stages in the development of a normoblast; *b*, the extrusion of the nucleus.

premyelocytes. They give rise to *myelocytes*, cells with round or crescentic nuclei and granular cytoplasm. Similar cells are developed in the lymphoid organs. By undergoing changes: (1) in the form and structure of their nuclei, and (2) in the size and staining qualities of their cytoplasmic granules, the myelocytes give rise to three types of granular leucocytes.

1. *Neutrophils* (70 to 72 per cent of all leucocytes). These have a finely granular cytoplasm which is neutral in its staining reactions, coloring by the interaction of both acid and basic stains. In development, their

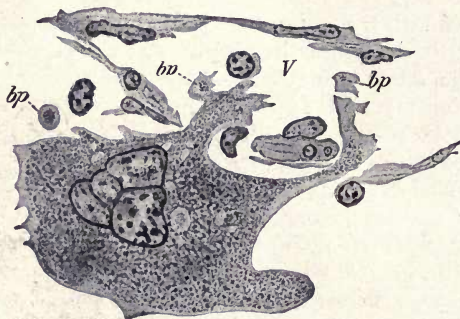


FIG. 253.—Giant cell from the bone marrow of a kitten, showing pseudopodia extending into a blood vessel (V), and giving rise to blood plates (bp) (Wright).

nuclei take up an eccentric position and become crescentic, horse-shoe shaped, and, in the older stages, lobate. As it changes in form, the nucleus undergoes pyknosis and stains intensely.

2. *Eosinophils* (2 to 4 per cent of all leucocytes). These are characterized by coarse cytoplasmic granules that stain intensely with acid dyes. In development the nucleus becomes bilobed.

It is commonly held that the eosinophilic granules differentiate endogenously (Downey, 1914). However, Weidenreich (1913) regards these granules as ingested fragments of red corpuscles or their hemoglobin derivatives. Badertscher (1913) found numerous eosinophils and free eosinophilic granules in the vicinity of degenerating muscle fibers in salamanders. Also, during trichiniasis in man, when there is extensive degeneration of muscle fibers, the number of eosinophils in the blood becomes greatly increased.

3. *Basophils* or *Mast Leucocytes* (0.5 per cent of all leucocytes). Their nuclei are very irregular in form and may be broken down into several pieces which stain intensely. The cytoplasmic granules are variable in number, size, and form, and often stain so heavily with basic dyes as to obscure the nucleus. Basophiles have been regarded as degenerating granular leucocytes, but at present this view is not generally accepted. They are apparently distinct from the 'mast cells' of the tissues.

Origin of the Blood Plates.—In the bone marrow and spleen pulp are *giant cells*, or *megakaryocytes*, the cytoplasm of which shows a darkly staining granular endoplasm and a clear hyaline ectoplasm (Fig. 253). It has been shown by Wright (1910) and others that the blood plates arise by being pinched off from cytoplasmic processes of the giant cells. The central granular mass of the plates represent portions of the endoplasm. Genuine blood plates and giant cells occur only in mammals.

DEVELOPMENT OF THE HEART

Vasculogenesis.—We have seen that the first blood cells and blood vessels take their origin in the angioblast, which develops in the wall of the yolk sac and chorion from the splanchnic mesoderm. The first vessels derived from the angioblast (see p. 243) are small, isolated blood spaces which unite and form capillary networks. From these, endothelial sprouts grow out, meet, and unite until complete networks are formed. In human embryos of 1 mm. or less, these envelop the lower portion of the yolk sac, the body stalk, and chorion.

There are two views as to the manner in which the heart and the primitive vascular trunks of the embryo originate. According to His and Rabl, and more recently Minot, Evans, and Bremer, all the blood vessels of the embryonic body arise as endothelial ingrowths from the extra-embryonic yolk-sac angioblast. Kölliker, Rückert, and Mollier (1906), on the contrary, assert that the intra-embryonic vessels are formed by the fusion of discrete anlagen in a way similar to that first occurring on the yolk sac. Corroborative investigations by Maximow, Huntington, Schulte, and others have shown that the apparent invasion of angioblast in reality represents a progressive fusion of isolated mesenchymal tissue spaces. Moreover, direct experimental proof on

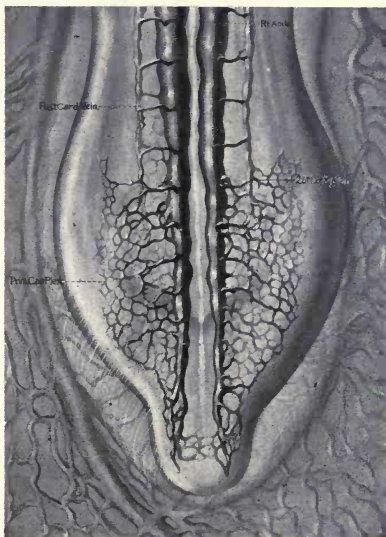


FIG. 254.—The caudal end of a chick embryo of 32 somites, showing the primary capillary plexus in the posterior limb buds from which the sciatic artery will differentiate. Aortæ have formed from the mesial margins of the plexuses (Evans).

living chick embryos (Miller; Reagan, 1915) leaves little doubt of the correctness of the Rückert-Mollier view.

The delicate injection methods of Mall and his students show that capillary plexuses precede the formation of definite arterial and venous trunks (Fig. 254). Only by the selection, enlargement, and differentiation

of appropriate paths do the definitive vessels arise. Capillaries, from which the flow has been diverted, atrophy. The primitive, paired aortæ are formed from the medial margins of such plexuses. Exceptions to the general rule are the intersegmental arteries which arise as single trunks from the aorta (Evans).

Inheritance, as well as the hydrodynamic factors incident to the blood flow, participates in the selection of channels from the capillary bed.

Origin of the Tubular Heart.—

The heart of the lower fishes and of amphibians arises in the ventral mesentery of the fore-gut. A tubular cavity first appears, about which the cells differentiate directly into endo-, myo-, and epicardium.

In bony fishes, reptiles, birds, and mammals, the heart is formed, while the embryo is still flattened on the surface of the yolk, from paired anlagen which later grow mesad and fuse. Aggregates of mesodermal cells, which soon form thin-walled tubes, first appear between the entoderm and splanchnic mesoderm; these are flanked by folds of splanchnic mesoderm that bulge laterally into the coelomic cavity (Figs. 255 A and 35). Such paired cellular masses (endothelial anlagen) are present in the Spee 1.54 mm. human embryo (Fig. 77). As the embryo grows away from the yolk and the fore-gut is formed, the entoderm withdraws from between the endothelial tubes, allowing these as well as the mesodermal folds to fuse (Figs. 255 B, C; 36 and 37).

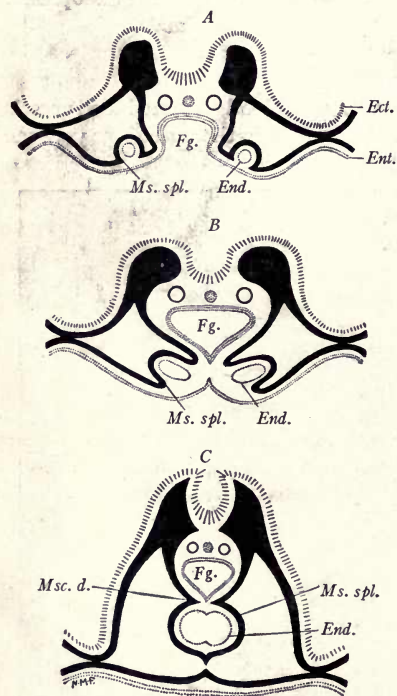


FIG. 255.—Diagrams to illustrate the origin of the mammalian heart. *Ect.*, Ectoderm; *End.*, endothelial tubes; *Ent.*, entoderm; *Fg.*, fore-gut; *Msc. d.*, dorsal mesocardium; *Ms. spl.*, splanchnic mesoderm (epi- and myocardium).

The heart is now an unpaired endothelial tube, lying in the folds of the splanchnic mesoderm (Fig. 190 A). Soon the ventral attachment of the mesoderm disappears, leaving the heart suspended by a temporary *dorsal mesocardium* in the single pericardial chamber (Fig. 255 C). The endothelial tube forms the *endocardium*, the splanchnic mesoderm later gives rise to the *epicardium* and *myocardium*. This type of heart occurs in human embryos of 2 mm. (5 or 6 somites, Fig. 256) and shows three regions: (1) the *atrium*, which receives the blood from the primitive veins; (2) the *ventricle*; (3) the *bulb*, from which is given off the *ventral aorta*.

As the cardiac tube grows faster than the pericardial cavity in which it lies, it bends to the right, the bulbus and ventricle forming a U-shaped loop (Fig. 257). Four regions may now be distinguished; (1) the *sinus venosus*; (2) the *atrium*, also thin-walled and lying cranial to the sinus; (3) the thick-walled *ventricular limb*, ventrad and caudad in position; (4) the *bulbar limb*, cranial to the ventricular limb and separated from it by the bulbo-ventricular cleft. Next, in

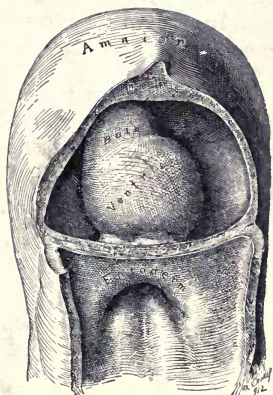


FIG. 256.—The heart of a 2 mm. human embryo in ventral view (Mall). $\times 65$. The open tube is the fore-gut.

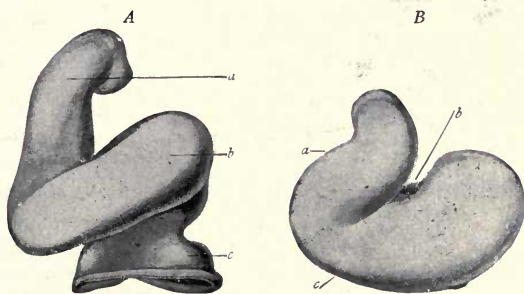


FIG. 257.—A, Heart of human embryo of 2.15 mm.: *a*, Bulbus cordis; *b*, primitive ventricle; *c*, atrial portion. B, Heart of human embryo of about 3 mm.: *a*, Bulbus cordis; *b*, atrial portion (behind); *c*, primitive ventricle (in front). Ventral views (His).

embryos of 3 to 4 mm., the bulbo-ventricular loop shifts its position until its base is directed caudad and ventrad (Fig. 257 B). At the same time the sinus venosus is brought dorsal to the atrium, which in turn is

cranial with relation to the bulbo-ventricular loop, and the bulbar limb is pressed against the ventral surface of the atrium and constricts it (Fig. 258 A).

In embryos of 4 to 5 mm. the right portion of the sinus venosus grows more rapidly than the left, this being due to the fact that the blood flow of

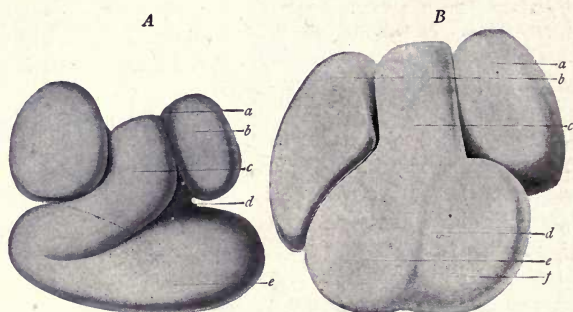


FIG. 258.—A, Heart of human embryo of about 4.3 mm.: *a*, Atrium; *b*, portion of atrium corresponding to auricular appendage; *c*, bulbus cordis; *d*, atrial canal; *e*, primitive ventricle. B, Heart of human embryo of about 10 mm.: *a*, Left atrium; *b*, right atrium; *c*, bulbus cordis; *d*, interventricular groove; *e*, right ventricle; *f*, left ventricle. Ventral views (His).

the left umbilical vein is shifted to the right side through the liver. As a result, the enlarged right horn of the sinus opens into the right dorsal wall of the atrium through a longitudinally oval foramen, guarded on the right by a vertical fold. This fold which projects into the atrium, is the *right*

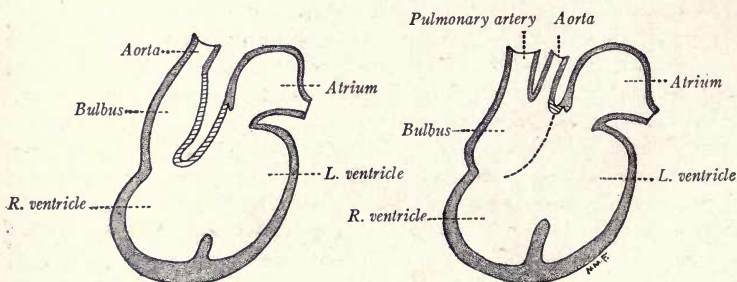


FIG. 259.—Diagrams to show the reduction of the bulbo-ventricular fold (represented by diagonal lines) due to its retarded development. (Modified after Keith.)

valve of the sinus venosus. Later, a smaller fold forms the *left valve of the sinus venosus* (Fig. 260 B). The atrium is constricted dorsally by the gut, ventrad by the bulbus. It therefore must enlarge laterally and in so doing forms the *right and left atria* (Fig. 258 A, B) with the distal portion of the

bulb between them. The deep, external groove between the atria and the bulbo-ventricular part of the heart is the *coronary sulcus*. As the bulbo-ventricular region increases in size, the duplication of the wall between the two limbs lags behind in development and finally disappears (Fig. 259), leaving the proximal portion of the bulb and the ventricular limb to form a single chamber, the *primitive ventricle*. In an embryo of 5 mm. the heart is thus composed of three undivided chambers: (1) the sinus venosus, opening dorsad into the right dilatation of the atrium; (2) the bilaterally dilated atrium, opening by the single transverse *atrial canal* into (3) the primitive, undivided ventricle. The three-chambered heart is persistent in adult fishes, but in birds and mammals a four-chambered heart is developed, in which venous blood circulates on the right side and arterial blood on the left. In amphibians and reptiles, transitional types occur.

The important changes next to be considered, leading to the formation of the four-chambered heart are: (1) the complete division of the atrium and ventricle, each into right and left chambers; (2) the division of the bulb and its distal continuation, the truncus arteriosus, into the aorta and pulmonary artery; (3) the incorporation of the sinus venosus into the wall of the right atrium; (4) the development of the semilunar and atrio-ventricular valves. The first of these changes is completed only after birth.

Origin of the Right and Left Atria.—In human embryos of 5 to 7 mm. there develops a thin, sickle-like membrane from the mid-dorsal wall of the atrium (Figs. 260 and 261). This is called the *atrial septum primum* (I). Simultaneously, endothelial thickenings appear in the dorsal and ventral walls of the atrial canal (Figs. 261 A, B). These are the *endocardial cushions*, which later fuse, thus dividing the single atrial canal into *right* and *left atrio-ventricular canals* (Fig. 266). The atrium is now partly divided into right and left atria, which, however, communicate ventrad through the *interatrial foramen*. Next, in embryos of 9 mm., the septum I thins out dorsad and cephalad and a second opening appears, the *foramen ovale* (Figs. 260 and 261 B). The atria are now connected by two openings, the interatrial foramen and the foramen ovale. Soon (embryos of 10 to 12 mm.), the ventral and caudal edge of septum I fuses with the endocardial cushions, which have in turn united with each other (Figs. 260 and 261 C). The interatrial foramen is thus obliterated, but the foramen ovale persists until after birth. In embryos of 9 mm. the *septum secundum* (II) is developed from the dorsal and cephalic wall of the atrium, just to the right of the septum primum (Fig. 260 C). It is important, as it later fuses with the left valve of the sinus venosus, whence the two form a great part of the atrial septum of the late fetal and adult heart.

Fate of the Sinus Venosus and its Valves.—The opening of the sinus venosus into the dorsal wall of the right atrium is guarded by two valves (Fig. 260). Along the dorsal and cephalic wall of the atrium these unite to form the *septum spurium*. Caudally the valves flatten out on the floor

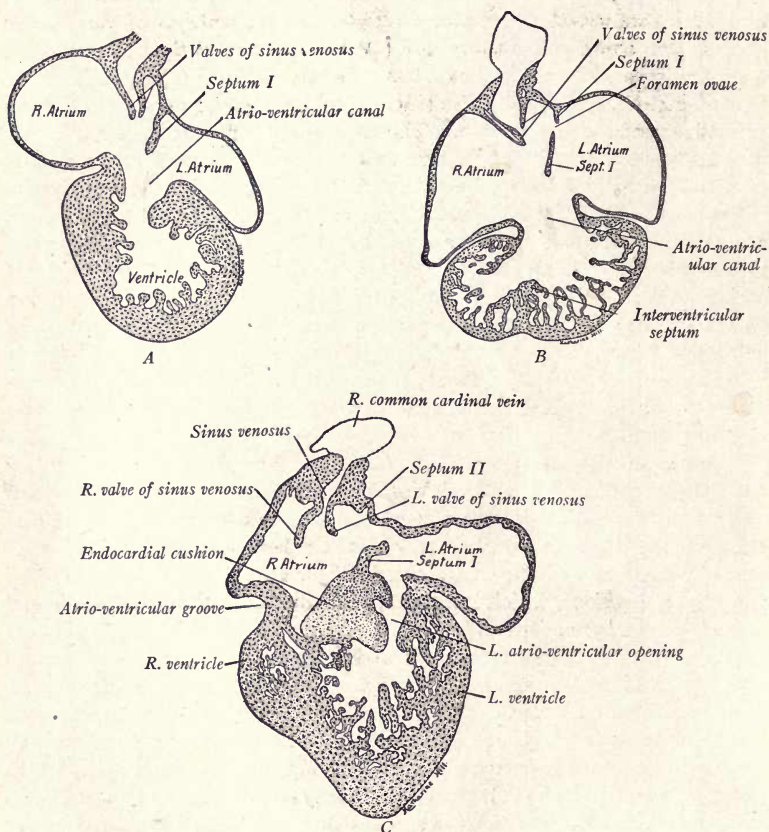


FIG. 260.—Horizontal sections through the chambers of the human heart: A, 6 mm.; B, 9 mm.; C, 12 mm. (A and B are based on figures of Tandler.) \times about 50.

of the atrium, but, as stated previously, the left valve later fuses with the atrial septum II. In embryos of 10 to 20 mm. the atria increase rapidly in size and the lagging right horn of the sinus venosus is taken up into the wall of the right atrium. By this absorption the superior vena cava

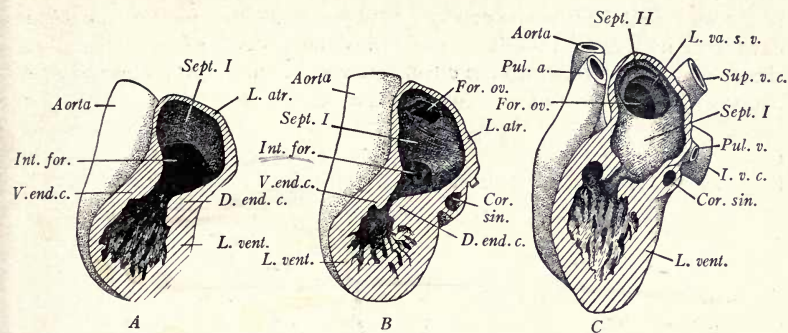


FIG. 261.—Lateral dissections of the human heart, viewed from the left side; A, 6 mm.; B, 9 mm.; C, 12 mm. (B is based on a reconstruction by Tandler). \times about 38. *Cor. sin.*, Coronary sinus; *D. end. c.*, dorsal endocardial cushion; *For. ov.*, foramen ovale; *Int. for.*, interatrial foramen; *I. v. c.*, inferior vena cava; *L. atr.*, left atrium; *L. va. s. v.*, left valve of sinus venosus; *L. vent.*, left ventricle; *Pul. a.*, pulmonary artery; *Pul. v.*, pulmonary vein; *Sept. I*, *Sept. II*, septum primum, septum secundum; *Sup. v. c.*, superior vena cava; *V. end. c.*, ventral endocardial cushion.

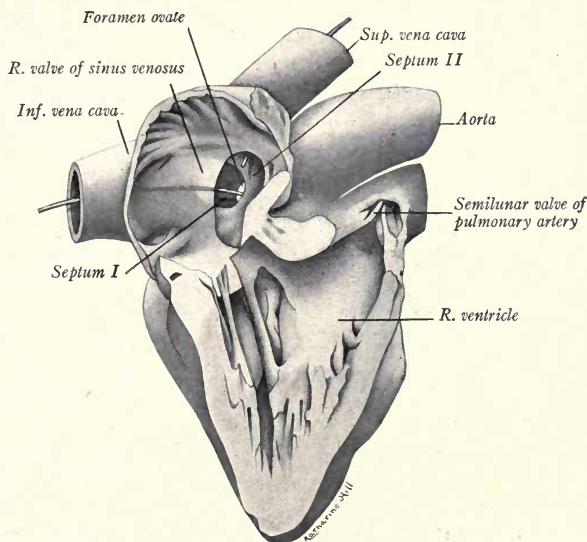


FIG. 262.—Lateral dissection of the heart of a 65 mm. human fetus, viewed from the right side. \times 12.

now opens directly into the cephalic wall of the atrium, the inferior vena cava into its caudal wall (Fig. 261 C). The transverse portion of the sinus venosus, persisting as the *coronary sinus* in part, opens into the posterior wall of the atrium.

The *right valve of the sinus venosus* is very high in 10 to 65 mm. embryos (first to third month) and nearly divides the atrium into two chambers (Fig. 262). It becomes relatively lower during the third and fourth

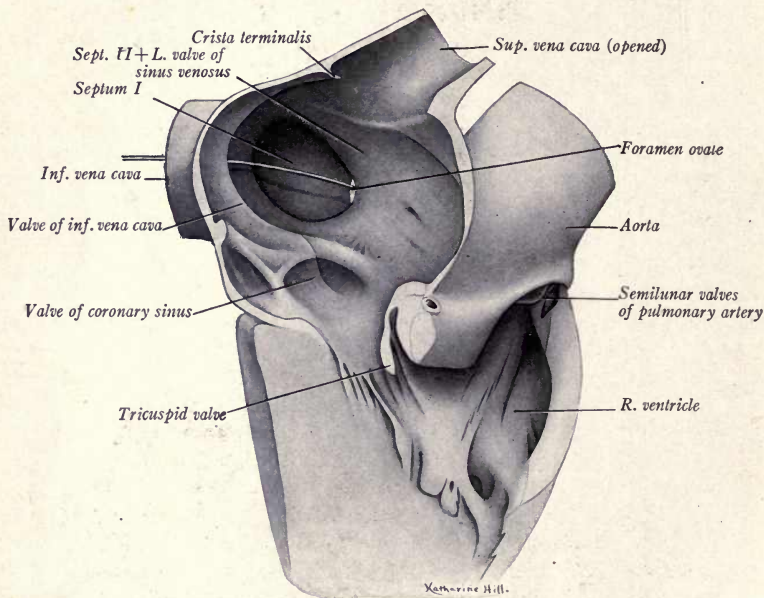


FIG. 263.—Lateral dissection of the heart of a 105 mm. human fetus, viewed from the right side.
× 7.

months. Its cephalic portion becomes the rudimentary *crista terminalis* (Fig. 263); the remainder is divided by a ridge into two parts, of which the larger cephalic division persists as the *valve of the inferior vena cava* (Eustachian valve) located at the right of the opening of the vein, and the smaller caudal portion becomes the *valve of the coronary sinus* (Thebesian valve).

The *left valve* of the sinus venosus unites with the septum II, and, in embryos of 20 to 22 mm. or larger, the two bound an oval opening (Figs. 263 to 265). The bounding wall of the oval aperture is the *limbus ovalis*.

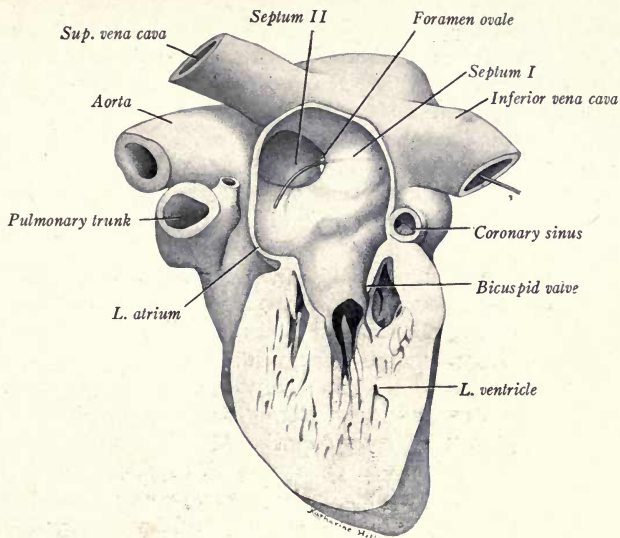


FIG. 264.—Lateral dissection of the heart of a 65 mm. human fetus, viewed from the left side, showing the septa and the foramen ovale. $\times 8$.

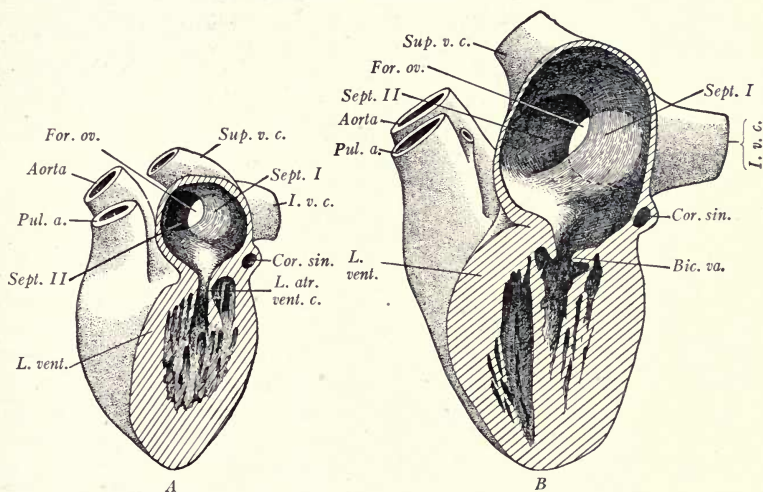


FIG. 265.—Lateral dissections of the human heart, viewed from the left side: *A*, from a 22 mm. embryo; *B*, from a 105 mm. fetus. *Bic. va.*, Bicuspid valve; *Cor. sin.*, coronary sinus; *For. ov.*, foramen ovale; *I.v.c.*, inferior vena cava; *L. atr. vent. c.*, left atrio-ventricular canal; *L. vent.*, left ventricle; *Pul. a.*, pulmonary artery; *Sept. I*, *Sept. II*, septum primum and septum secundum.

Closure of the Foramen Ovale.—The free edge of the septum I is, in embryos of 10 to 15 mm., directed dorsad and cephalad (Fig. 261 C). Gradually, in later stages (Figs. 264 and 265), its caudal and dorsal prolongation grows cephalad and ventrad until its free edge is so directed. Coincident with this change, the septum II, with its free edge directed at first ventrad and caudad, shifts until its free edge is directed dorsad and cephalad, and overlaps the septum I (Figs. 261 C, 264 and 265). The opening between these septa persists until after birth as the *foramen ovale*.

During fetal life the left atrium receives little blood from the lungs, so that the pressure is much greater in the right atrium. As a result, the septum I is pushed to the left and the blood flows from the right into the left atrium through the foramen ovale. After birth, the left atrium receives from the expanding lungs as much blood as the right atrium, the septum I is pressed against the limbus of the previously fused septum II and left sinus valve, and unites with it. The depression formed by the thinner walled septum I is the *fossa ovalis*.

The Pulmonary Veins.—In embryos of 6 to 7 mm., a single vein (arising in the cat from a peripulmonary plexus, Brown, 1913) drains into the caudal wall of the left atrium at the left of the septum I (Fig. 261 C). This vein bifurcates into right and left pulmonary veins which divide again before entering the lungs. As the atrium grows, the proximal portion of the pulmonary vein is taken up into the atrial wall. As a result, at first two, then four pulmonary veins open into the left atrium.

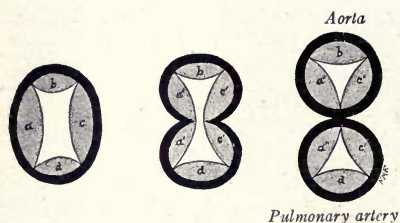


FIG. 266.—Scheme showing division of bulbus cordis and its thickening into aorta and pulmonary artery with their valves. (Explanation in text.)

Origin of the Aorta and Pulmonary Artery.

In embryos of 4 to 6 mm. there arise in the aortic bulb (including its distal truncus arteriosus) longitudinal thickenings, *four in the distal half, two in the proximal half*. Of the four *distal* thickenings (Fig. 266), two, which may be designated *a* and *c*, are larger than the other thickenings, *b* and *d*. Thickenings *a* and *c*, which distally occupy left and right positions in the bulb, meet, fuse, and divide the bulb into a dorsally placed aorta and ventrally placed pulmonary trunk (Fig. 267). Traced proximally they pursue a clockwise, spiral course, *a* shifting from left to ventral, and *c* from right to dorsal, both becoming continuous with the proximal swellings. Thickenings *b* and *d* are also prominent at one point

proximally; when the bulb in this region is divided by ingrowing connective tissue into the aorta and pulmonary artery, the aorta contains the whole of the thickenings *b* and half of *a* and *c*, while the pulmonary

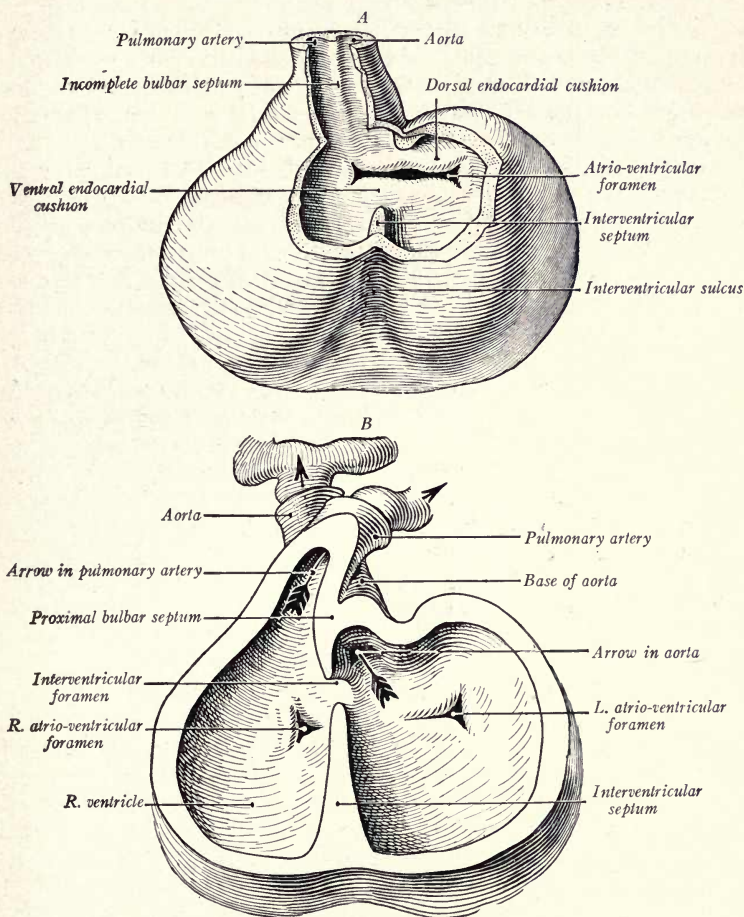


FIG. 267.—Stages of the human heart, in ventral view, to show the division of the bulbus and ventricle: A, 5 mm. embryo; B, 7.5 mm. embryo.

trunk contains the whole of *d* and half of *a* and *c* (Fig. 266). Distally, the three thickenings now present in each vessel disappear, but proximally they enlarge, hollow out on their distal surfaces, and eventually

form the thin-walled *semilunar valves* (Fig. 266). The anlagen of these valves are prominent in embryos of 10 to 15 mm. as plump swellings projecting into the lumina of the aorta and pulmonary artery.

The two *proximal* bulbar swellings fuse and continue the spiral division of the bulb toward the interventricular septum in such a way that the base of the pulmonary trunk, now ventrad and to the right, opens into the right ventricle, while the base of the aorta, now lying to the left and dorsad, opens into the left ventricle close to the interventricular foramen, through which the two ventricles still communicate (Fig. 267 B).

Origin of the Right and Left Ventricles.—Coincident with the division of the aortic bulb there appears at the base of the primitive ventricular cavity a sagittally placed elevation, the *interventricular septum*. (Fig. 260 B). It later grows cephalad and dorsad toward the endocardial cushions, and forms an incomplete partition between the right and left ventricles, which still communicate through the persisting *interventricular foramen* (Fig. 267 B). Corresponding to the internal attachment of the septum there is formed externally the *interventricular sulcus* (Fig. 267 A); this marks the external line of separation between the large left ventricle and the smaller right ventricle. The *interventricular foramen* in embryos of 15 to 16 mm. is bounded: (1) by the interventricular septum; (2) by the proximal bulbar septum; and (3) by the dorsal portion of the fused endocardial cushions (Fig. 267). Soon these structures are approximated and fuse, thereby forming the *septum membranaceum*, which closes the interventricular foramen.

The *atrio-ventricular* valves arise as thickenings of the endocardium and endocardial cushions about the atrio-ventricular foramina (Figs. 260 and 261). Three such thickenings are formed on the right, two on the left. The anlagen of the valves are at first thick and project into the ventricles. Later, as the ventricular wall differentiates, the valvular anlagen are undermined, leaving their edges attached to the ventricular walls by muscular *trabeculae*, or cords. The muscle tissue of both the valves and *trabeculae* soon degenerates and is replaced by connective tissue, forming the *chordae tendineae* of the adult valves. Thus there are developed the three cusps of the *tricuspid valve* between the right chambers of the heart, and the two flaps of the *bicuspid*, or *mitral valve*, between the left atrium and left ventricle.

Differentiation of the Myocardium.—The myocardium, at first uniformly spongy, becomes compact at the periphery. The inner bundles remain trestle-like, forming the *trabeculae carneae* and the *papillary* and *moderator muscles* around all of which the originally simple endocardial sac is wrapped. The myocardial layers, at first continuous over the surface of the heart, become divided by connective tissue at the atrio-ventricular canal, leaving a small bridge alone. This connecting strand, located behind the posterior endocardial cushion, forms the *atrio-ventricular bundle*.

Descent of the Heart.—At first the heart lies far cephalad in the cervical region, but it gradually recedes during development until it assumes its permanent position in the thorax.

Anomalies.—Dextrocardia is associated with a general transposition of the viscera (p. 195). The aorta and pulmonary artery may also be transposed in the absence of dextrocardia. Rarely the paired anlagen form a double heart. Of the complete or partial defects of the septa, most common is a patent foramen ovale. If this fails to close after birth, the mixed blood produces a purplish hue in the child which is known popularly as a 'blue baby'. This condition may be persistent in adult life. Incomplete closure occurs in about one in four cases, but actual mingling of the blood is rare, due to an approximation of the overlapping septal folds during atrial systole.

THE PRIMITIVE BLOOD VASCULAR SYSTEM

The first paired vessels of human embryos are formed as longitudinal anastomoses of capillary networks, that originate first in the angioblast of the yolk sac and chorion (p. 243). In the Eternod embryo of 1.3 mm., in which the somites are still undeveloped, such paired vessels are already formed (cf. Fig. 268). The *umbilical veins* emerge from the chorion, fuse in the body stalk, then, separating, course in the somatopleure

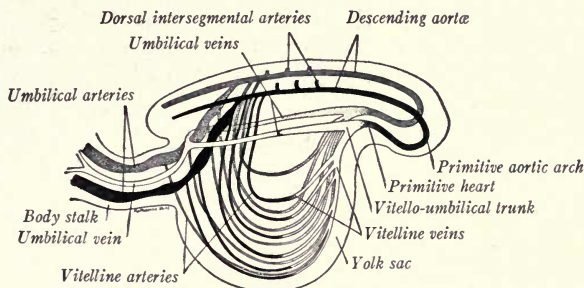


FIG. 268.—Diagram, in lateral view, of the primitive blood vessels in human embryos of 1.5 to 2 mm.

to the paired, tubular heart anlagen. From the heart tubes, paired vessels, the *ventral aortæ*, extend cephalad, then bend dorsad as the first aortic arches and extend caudad as the *descending aortæ*. These, as the *umbilical arteries*, bend sharply ventrad into the belly stalk and branch in the wall of the chorion. The chorionic circulation is thus the first to be established.

In embryos 2 to 2.5 mm. long (5 to 8 somites), the heart has become a single tube (Fig. 269). From the yolk sac, numerous veins converge cephalad and form a pair of *vitelline veins*. These join the umbilical veins, and, as the *vitello-umbilical trunks*, traverse the septum transversum and open into the sinus venosus. The descending *aortæ* give off, dorsally and cranially, several pairs of dorsal *intersegmental arteries*, and, ventrad and

caudad, a series of *vitelline arteries* to the yolk sac. The umbilical arteries now take their origin from a plexus of ventral vessels in series with the vitelline arteries. At this stage the vitelline circulation of the yolk sac is established.

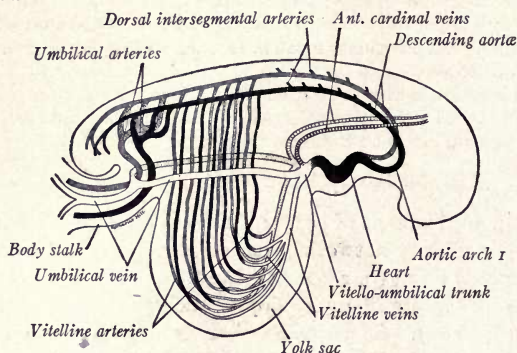


FIG. 269.—Diagram, in lateral view, of the primitive blood vessels in human embryos of 2 to 2.5 mm

In embryos of 15 to 23 somites (Fig. 270) the *veins* of the embryo proper develop as longitudinal anastomoses of branches from the segmental arteries. The paired *anterior cardinal veins* of the head are developed first,

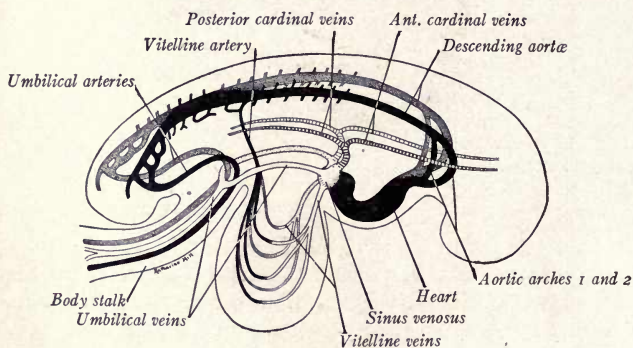


FIG. 270.—Diagram of the blood vessels of a human embryo of 2.6 mm.

and, coursing back on either side of the brain, they join the vitello-umbilical trunk. In embryos of 23 somites, the *posterior cardinals* are present. They lie dorsal to the nephrotomes, and, running cephalad, join the anterior cardinal veins to form the *common cardinal veins*. Owing to the later enlargement of the sinus venosus, the proximal portions of the com-

mon venous trunks are taken up into its wall, and thus three veins open into each horn of the sinus venosus: (1) the *umbilical veins* from the chorion; (2) the *vitelline veins* from the yolk sac; (3) the *common cardinal veins* from the body of the embryo.

The *descending aortæ* have now fused caudal to the seventh intersegmental arteries and form the single *dorsal aorta* as far caudad as the origin of the umbilical arteries.

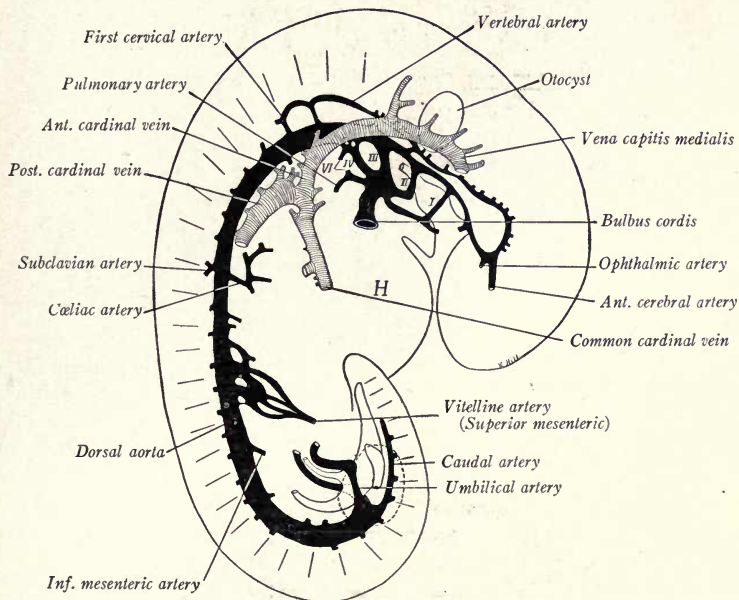


FIG. 271.—Arteries and cardinal veins of the right side in a 4.9 mm. human embryo (modified after Ingalls). $\times 20$. H, Heart; I–VI, aortic arches.

Of the numerous *vitelline arteries* one pair is prominent; it fuses into a single vessel which courses in the mesentery and later becomes the *superior mesenteric artery*. By the enlargement of capillaries connecting the ventral and dorsal aortæ, a second pair of *aortic arches* is formed at this stage (Fig. 270).

In embryos 4 to 5 mm. in length, five pairs of aortic arches are successively developed: the first, second, third, fourth, and sixth (Fig. 271). An additional pair of transitory vessels, which extend from the ventral aorta to the sixth arch, appear later in embryos of 7 mm., but soon degenerate (Fig. 272 B). They are interpreted as being the

fifth pair in the series. From each dorsal, or descending aorta there develop cranially the *internal carotid arteries*. These extend toward the optic stalks where they bend dorsad and caudad, connecting finally with the first intersegmental arteries of each side (Fig. 271). The descending aortæ are now fused to their extreme caudal ends and the umbilical arteries take their origin ventrally. Twenty-seven pairs of dorsal *intersegmental arteries* are present. From the seventh cervical pair of these the *subclavian arteries* of the upper limbs arise. Of the ventral vitelline vessels three are now prominent: the *celiac artery* in the stomach-pancreas region, the *vitelline*, or *superior mesenteric*, in the small intestine region, and the *inferior mesenteric* of the large intestine region.

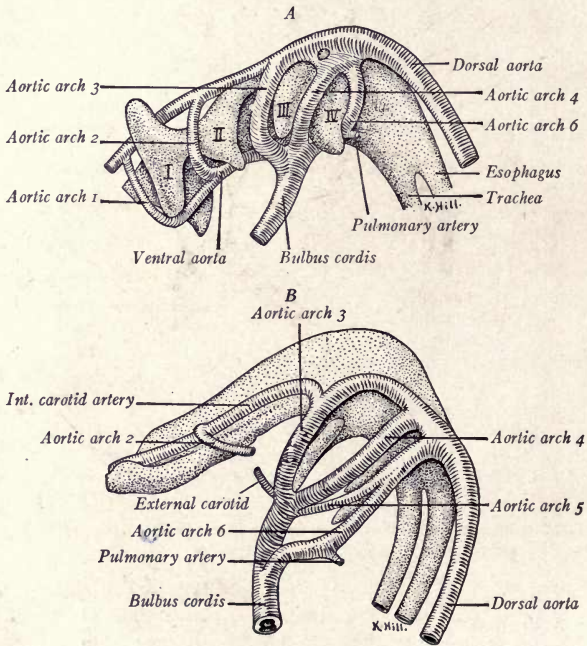


FIG. 272.—Aortic arches of human embryos: A, of 5 mm.; B, of 7 mm. (after Tandler). I–IV, pharyngeal pouches.

DEVELOPMENT OF THE ARTERIES

Transformation of the Aortic Arches.—The ancestral aortic arches are early transformed into more appropriate vessels. The third pair is largest at 5 mm. (Fig. 272, A); at 7 mm. the first and second aortic arches (are obliterated (Figs. 272 B and 273), but the descending and

ventral aortæ cranial to the third arch persist as parts of the *internal* and *external carotid* arteries respectively. The third arches form the stems of the internal carotids, while the ventral aortæ between the third and fourth arches become the *common carotids*. In embryos of 15 mm. the bulbus cordis has been divided into the aortic and pulmonary trunks, so that the aorta opens into the left ventricle and the pulmonary trunk into the right ventricle. The descending aortæ between the third and fourth arches disappear, but the fourth arch on the left side persists as the *aortic arch* of the adult. On the right side, the fourth aortic arch persists with the descending aorta as far as the seventh

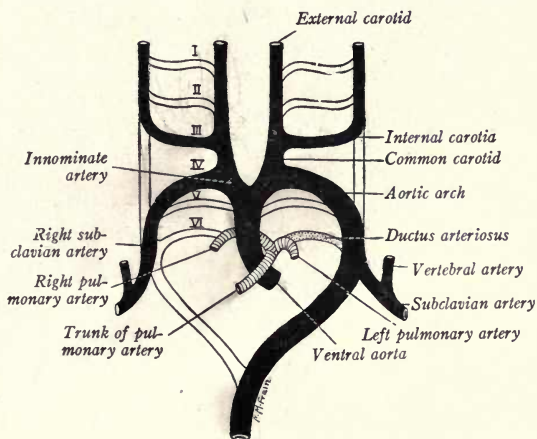


FIG. 273.—Diagram showing the aortic arches and their derivatives in human embryos.

intersegmental artery and forms part of the *right subclavian artery*, which is thus a more complex vessel than the left. The segment of the fourth arch proximal to the right common carotid becomes the *innominate artery*. The fifth arches of amniotes are rudimentary (p. 100). On the right side, the sixth arch between the origin of the right pulmonary artery and descending aorta is early lost; on the left side, it persists as the *ductus arteriosus* and its lumen is only obliterated after birth. The proximal portion of the right sixth arch forms the stem of the *right pulmonary artery*, but the proximal portion of the left arch is incorporated in the pulmonary trunk. Most of the pulmonary artery arises from a post-branchial plexus; union with the sixth arch is acquired secondarily (Huntington, 1919).

The aortic arches of the embryo are of especial importance comparatively. Five arches are formed in connection with the gills of adult fishes. In adult tailed amphibia,

three or four arches, and in some reptiles two arches, are represented on either side. In birds the right, in mammals the left fourth arch persists as the arch of the aorta.

The different courses of the *recurrent laryngeal nerves* are easily explained. The vagus early gives off paired branches which reach the larynx by passing caudal to the primitive fourth aortic arches. When the latter, through growth changes, descend into the chest, loops of both nerves are carried with them. Hence, after the transformation of the fourth arches, the left recurrent nerve remains looped around the arch of the aorta, the right around the right subclavian artery (cf. Fig. 273).

Branches of the Dorsal Aorta.—From the primitive aortæ arise: (1) *dorsal*, (2) *lateral*, and (3) *ventral branches* (Fig. 274).

1. The *dorsal branches* are intersegmental and develop small dorsal and large ventral rami. From the *dorsal rami* are given off neural branches which bifurcate and form dorsal and ventral *spinal arteries*.

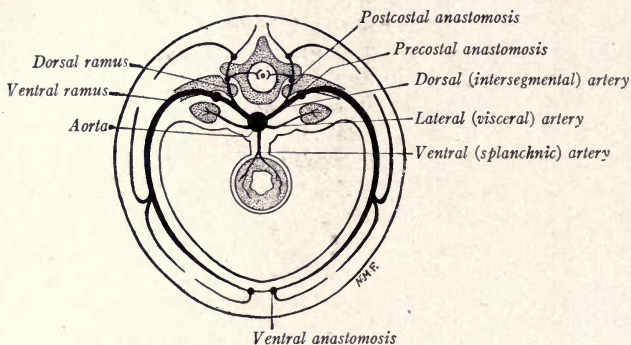


FIG. 274.—Diagram of the trunk, in transverse section, showing the arrangement of the aortic branches.

As we have seen (Fig. 271), the internal carotids are recurved cranially in the 5 mm. embryo and anastomose with the first two pairs of dorsal intersegmental arteries. By longitudinal postcostal anastomoses (Fig. 274) of the *dorsal rami* of the first seven pairs of dorsal intersegmental arteries, the *vertebral arteries* arise (Fig. 275). The original trunks of the first six pairs are lost, so that the vertebrals take their origin with the *subclavians* from the *seventh pair* of intersegmental arteries (Fig. 276). In embryos of 9 mm. the vertebrals in the region of the metencephalon fuse to form a single, median ventral vessel, the *basilar artery*, which thus is connected cranially (by way of the *circulus arteriosus*) with the internal carotids, caudad with the vertebral arteries.

The internal carotids (Fig. 271), after giving off the *ophthalmic arteries*, give rise cranially to the *anterior cerebral artery*, from which arise later the *middle cerebral artery*

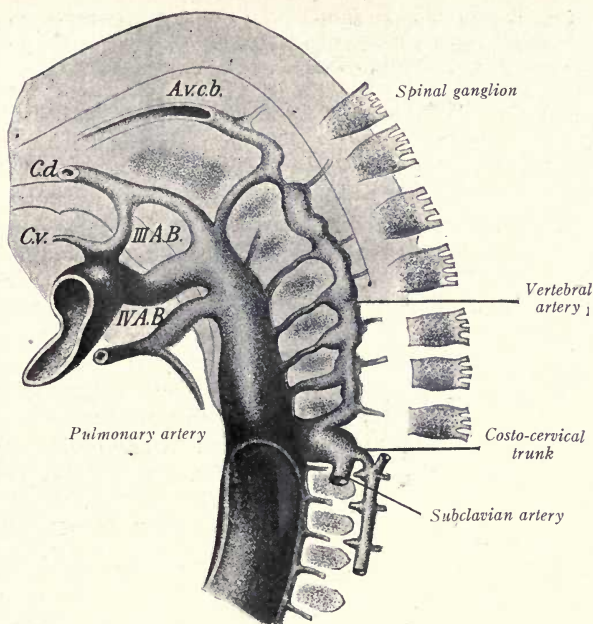


FIG. 275.—The development of the vertebral and subclavian arteries and the costo-cervical trunk in a young rabbit embryo (modified after Hochstetter). *III AB.-IV AB.*, Aortic arches; *A.v.c.b.* cephalic portion of vertebral artery; *C.d.* and *C.v.*, internal and external carotid arteries.

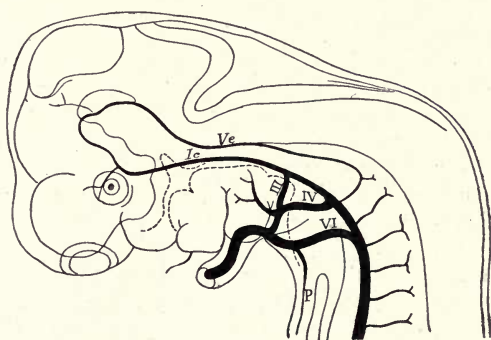


FIG. 276.—Arterial system of a human embryo of 10 mm. (His). $\times 18$. *Ic*, Internal carotid artery; *P*, pulmonary artery; *Ve*, vertebral artery; *III-VI*, persistent aortic arches.

and the *anterior chorioidal artery*; all of these supply the brain. Caudalward many small branches to the brain wall are given off, and, quite late in development (48 mm. C R), they form a true *posterior cerebral artery* (Mall).

The *ventral rami* of the dorsal intersegmental arteries become prominent in the thoracic and lumbar regions and persist as the *intercostal* and *lumbar arteries*, segmentally arranged in the adult. Longitudinal precostal anastomoses (Fig. 274) constitute the *costo-cervical* and *thyreo-cervical trunks* (Fig. 275). The *subclavian* and a portion of the *internal mammary artery* are derived from the ventral ramus of the seventh cervical segmental artery. The remainder of the internal mammary and the *superior* and *inferior epigastric arteries* are formed by longitudinal ventral anastomoses (Fig. 274) between the extremities of the ventral rami from the thoracic and lumbar intersegmental arteries, beginning with the second or third thoracic (Fig. 277).

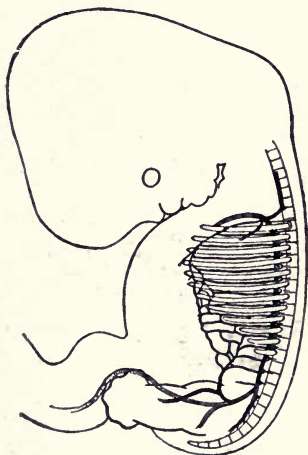


FIG. 277.—The development of the internal mammary and deep epigastric arteries in a human embryo of 13 mm. (Mall in McMurrich).

2. The *lateral (visceral) branches* of the descending aortæ are not segmentally arranged. They supply structures arising from the nephrotome region (mesonephros, sexual glands, metanephros, and suprarenal glands). From them later arise the *renal*, *suprarenal*, *inferior phrenic*, and *internal spermatic* or *ovarian arteries*.

3. The *ventral (splanchnic) branches* are at first rather definitely intersegmental. Primitively they form the paired vitelline arteries to the yolk sac (Figs. 268 to 270). Coincident with the degeneration of the yolk sac the prolongations of the ventral vessels to its walls disappear, and the paired persisting arteries, passing in the mesentery to the gut, fuse to form unpaired vessels from which three large arteries are derived: the *cæliac artery*, the *superior mesenteric*, and the *inferior mesenteric* (Fig. 271).

The primitive cæliac axis arises opposite the seventh intersegmental artery. Together with the mesenteric arteries, it migrates caudalward until eventually its origin is opposite the twelfth thoracic segment (Mall). This migration, according to Evans, is due to the unequal growth of the dorsal and ventral walls of the aorta. Similarly, the superior mesenteric artery is displaced caudad ten segments, the inferior mesenteric artery three segments.

The Umbilical and Iliac Arteries.—As previously described, the umbilical arteries arise in young embryos of 2 to 2.5 mm. from the primitive aortæ opposite the fourth cervical segment. They take origin from a plexus of ventral vessels of the vitelline series (Fig. 270), and are gradually shifted caudad until they arise from the dorsal aorta opposite the twenty-third segment (fourth lumbar). In 5 mm. embryos, the umbilical arteries develop secondary *lateral* connections with the aorta (Fig. 278 A). The new vessels pass lateral to the mesonephric ducts, and, in 7 mm. embryos, the primitive ventral stem-artery has disappeared. The segment of this

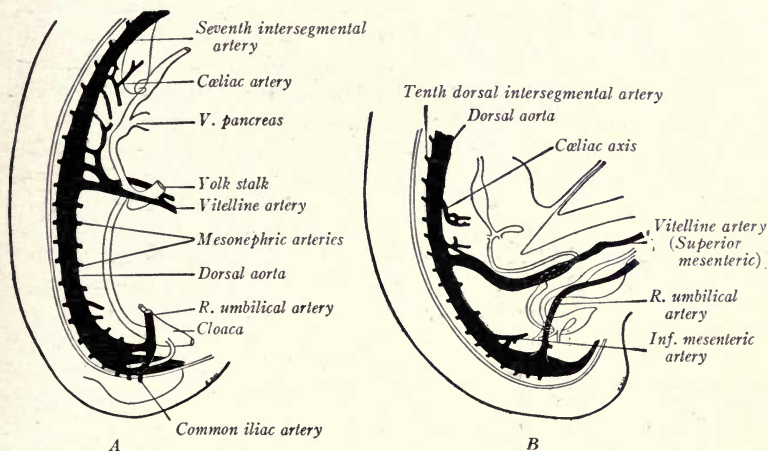


FIG. 278.—Reconstructions, showing the development of the umbilical and iliac arteries (after Tandler): A, 5 mm. human embryo; B, 9 mm. human embryo.

new trunk, proximal to the origin of the *external iliac artery* which soon arises from it, becomes the *common iliac*. The remainder of the umbilical trunk constitutes the *hypogastric artery*. When the placental circulation ceases at birth, the distal portions of the hypogastric arteries, from pelvis to umbilicus, atrophy, forming the solid *obliterated hypogastric arteries* of adult anatomy.

The *middle sacral artery* is the direct caudal continuation of the aorta. Its dorsal position is the result of secondary growth changes.

Arteries of the Extremities.—It is assumed that in man, as in observed birds and mammals, the first vessels of the limb buds form a capillary plexus.

Upper Extremity.—The capillary plexus takes origin by several lateral branches from the aorta. In human embryos of 5 mm. but one connecting vessel remains, and this takes its origin secondarily from the seventh dorsal intersegmental artery, forming the ventral ramus of this artery and its lateral offset (Fig. 274). The portion of this vessel in what will

become the free arm is plexiform at first, but later becomes a single stem which forms successively the *subclavian*, *axillary*, *brachial*, and *interosseous arteries*. Subsequently the *median*, *radial*, and *ulnar arteries* of the arm are formed.

Lower Extremity.—In embryos of 7 mm. there is given off from the secondary lateral trunk of the umbilical artery (i. e., from the future common iliac) a small branch which forms the chief arterial stem of the lower extremity, the future *popliteal* and *peroneal arteries*. This, the *arteria ischiadica*, is superseded in embryos of 15.5 mm. by the *external iliac* and *femoral arteries*, of which the latter annexes the branches of the ischiadic distal to the middle of the thigh. The *arteria ischiadica* persists proximally as the *inferior gluteal artery*.

DEVELOPMENT OF THE VEINS

We have seen that in embryos of 23 somites three systems of paired veins are present: the *umbilical veins* from the chorion, the *vitelline veins* from the yolk sac, and the *anterior* and *posterior cardinal veins*, which unite in the *common cardinal veins*, from the body of the embryo. Thus, three veins open into the right horn of the sinus venosus, and three into the left (Fig. 270).

Changes in the Vitelline and Umbilical Veins.—*Vena portæ.*—With the increase in size of the liver anlagen there is an intercrescence of the hepatic cords and the endothelium of the vitelline veins. As a result, these veins form in the liver a network of sinusoids (Fig. 279), and each vein is divided into a *distal portion* which passes from the yolk sac to the liver, and into a *proximal portion* which carries blood from the liver sinusoids to the sinus venosus. Soon the proximal portion of the left vitelline vein is largely absorbed into the sinusoids of the liver and shifts its blood flow into the right horn of the sinus venosus. In the meantime the liver tissue grows laterally, comes into contact with the umbilical veins, and taps them so that their blood flows more directly to the heart through the sinusoids of the liver (Fig. 280). As the channel of the right proximal vitelline is larger, the blood from the left umbilical vein flows diagonally to the right horn of the sinus venosus. When all the umbilical blood enters the liver, as in embryos of 5 to 6 mm., the proximal portions of the umbilical veins atrophy and disappear (Fig. 281). In 5 mm. embryos the vitelline veins have formed three cross anastomoses with each other (Figs. 280 and 281): (1) a cranial transverse connection in the liver, ventral to the duodenum; (2) a middle one, dorsal to the duodenum; and (3) a caudal one, ventral to it. There are thus formed about the gut a cranial and a caudal venous ring. In embryos of 7 mm. the left umbilical vein has enlarged, while the corresponding right vein has degenerated. Of the two venous loops, only the right limb of the cranial ring and the left limb of the caudal ring, together with the median dorsal anastomosis, persist. A new vein the *superior mesenteric*, develops in the mesentery of the intestinal loop and joins the left vitelline vein just caudal to its dorsal middle

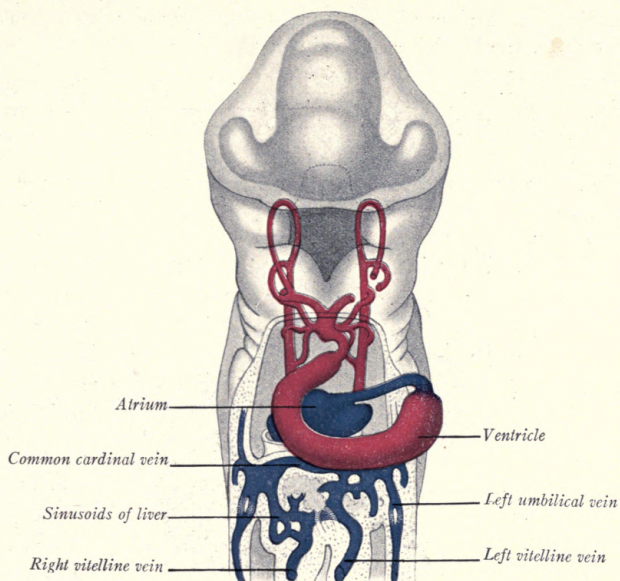


FIG. 279.—Reconstruction of the blood vessels of a 4.2 mm. human embryo in ventral view (His)

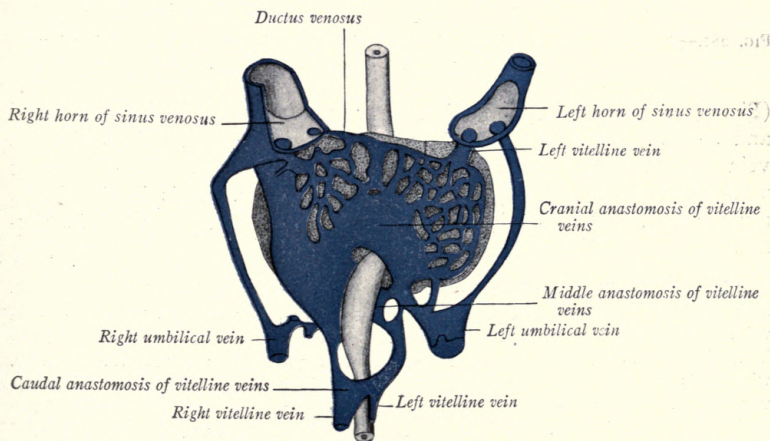


FIG. 280.—Reconstruction of the veins of the liver in a 4.9 mm. human embryo (after Ingalls).

anastomosis with the right vitelline vein. Subsequently, with the atrophy of the yolk sac, the left vitelline vein degenerates caudal to its junction with the superior mesenteric vein. The persisting trunk between the superior mesenteric vein and the liver is the *vena portæ*, and thus represents: (1) a portion of the left vitelline vein in the left limb of the caudal ring; (2) the middle transverse anastomosis between the vitelline veins; (3) the portion of the right vitelline vein which forms the right limb of the cranial ring.

In the liver, the portal vein, through its cranial anastomosis between the primitive vitelline veins, is connected with the left umbilical vein

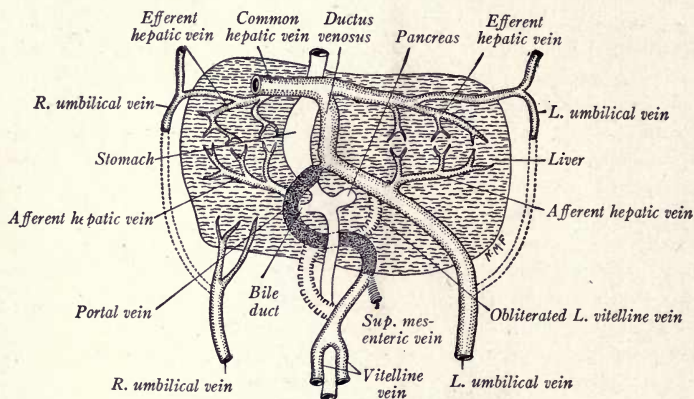


FIG. 281.—A diagram showing the development of the portal vein as illustrated in a human embryo of about 7 mm. (modified after His).

(Fig. 281). As the right lobe of the liver grows, the course of the umbilical and portal blood through the intrahepatic portion of the right vitelline vein becomes circuitous, and hence a new, direct channel to the sinus venosus is formed through the hepatic sinusoids. This is the *ductus venosus* (Fig. 281), which is obliterated after birth and forms the *ligamentum venosum* of the postnatal liver.

According to Mall, the intrahepatic portion of the right vitelline vein persists proximally as the *right ramus* of the hepatic vein, and distally as the *ramus arcuatus* of the portal vein. The intrahepatic portion of the left vitelline vein drains secondarily into the right horn of the sinus venosus, and proximally forms later the *left hepatic ramus*. Distally, where it is connected with the left umbilical vein, it becomes the *ramus angularis* of the *vena portæ*. In this way two primitive portal, or supplying trunks, and two hepatic, or draining trunks, originate. Later there are differentiated first four, then six, such opposed trunks within the liver, and the six primary lobules supplied and drained by these trunks may be recognized in the adult liver.

Of the umbilical veins, the right disappears early; the left persists during fetal life, shifts to the median plane, and courses in the free edge of the falciform ligament. After birth its lumen is closed, and from the umbilicus to the liver it forms the *ligamentum teres*. In early stages, veins from the body wall drain into the umbilical veins.

The Anterior Cardinal Veins and the Origin of the Superior Vena Cava.—The anterior cardinal veins consist each of two parts (Fig. 271): (1) the true anterior cardinals, located laterad in the segmented portion of the head and neck and draining into the common cardinal veins; (2) the *vena capitis medialis*, extending into the unsegmented head proper and running ventro-lateral to the brain wall. In embryos of 20 mm. there has formed by anastomosis a large connection between the right and left anterior cardinals, which carries the blood from the left side of the head into the right vein (Fig. 282 C). Soon, the left anterior cardinal loses its connection with the common cardinal on the left side; the remaining portions become the *accessory hemiazygos* and the inconstant *oblique vein of the left atrium* (Fig. 282 D). The proximal portion of the left common cardinal, with the transverse portion of the sinus venosus, persists as the *coronary sinus*. The right common cardinal and the right anterior cardinal vein, as far as its anastomosis with the left anterior cardinal become the *superior vena cava*. The anastomosis itself forms the *left vena anonyma*, while that portion of the right anterior cardinal between the anastomosis and the right subclavian vein is known as the *right vena anonyma*. The distal portions of the anterior cardinals become the *internal jugular veins* of the adult, while the *external jugular* and *subclavian veins* are new vessels which develop somewhat later.

The *vena capitis medialis* (Fig. 271) is the continuation of the anterior cardinal vein into the head of the embryo, where at first it lies mesial to the cerebral nerves. Later, it is partly shifted by anastomoses lateral to the cerebral nerves and forms the *vena capitis lateralis* (Figs. 283 and 284). In 11 mm. embryos this emerges with the n. facialis, and, caudal to the n. hypoglossus, becomes the *internal jugular*. Cranially, in the region of the fifth nerve, the median vein of the head persists as the *sinus cavernosus* and receives the *ophthalmic vein* from the eye and the *anterior cerebral vein* from the fore- and mid-brain regions (Fig. 284 C). Between the n. trigeminus and the facialis, the *middle cerebral vein* from the metencephalon (cerebellum) joins the v. capitis lateralis before it leaves the cranium. More caudally, the *posterior cerebral vein* from the myelencephalon emerges through the jugular foramen and is drained with the others by the v. capitis lateralis into the internal jugular (Fig. 284 B). Soon, the cerebral veins reach the dorsal median line (Fig. 284 C), and longitudinal anastomoses are formed: (1) between the anterior and middle cerebral veins, giving rise to the *superior sagittal sinus*; and (2) between the middle and posterior cerebral veins forming the greater part of the *transverse sinuses*. In embryos of 33 mm. the v. capitis lateralis disappears and the blood from the brain passes through the superior sagittal and lateral sinuses and is drained by way of the jugular foramen into the internal jugular vein (Fig. 284 C, D). The middle cerebral vein becomes the *superior*

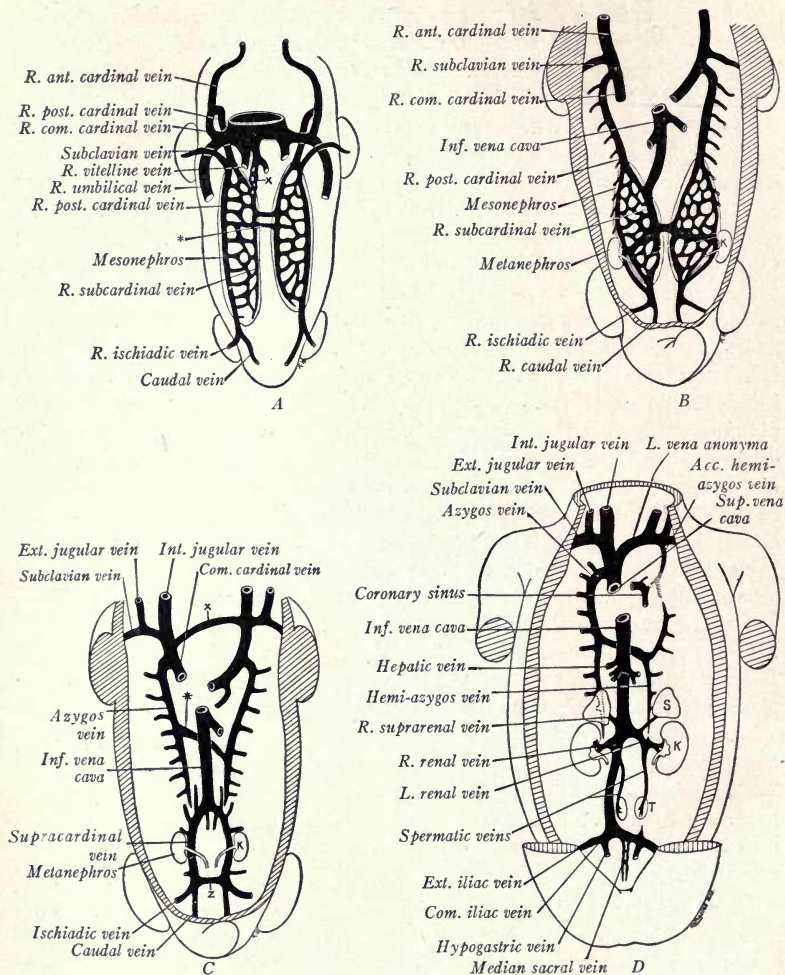


FIG. 282.—Four diagrams showing the development of the superior and inferior venae cavae and the fate of the cardinal veins (modified after Kollmann). X, in A, vein of the plica venae cavæ; *, anastomosis between subcardinal veins; X, in C, anastomosis between anterior cardinal veins which forms the left vena anonyma; *, in C, cranial anastomosis between the azygos veins; z, caudal anastomosis between supracardinal veins; K, kidney; S, suprarenal gland; T, testis.

petrosal sinus, but the *inferior petrosal sinus* is formed as a new channel median to the internal ear. The anterior cerebral vein becomes the *superficial middle cerebral* of adult anatomy. A more detailed account of these changes may be found in the original work of Mall (Amer. Jour. Anat., vol. 4, 1905).

The Posterior Cardinal Veins and the Origin of the Inferior Vena Cava.—The posterior cardinal veins course cephalad along the dorsal sides of the mesonephroi and open into the common cardinal veins (Fig. 282 A). Each receives an *ischiodic vein* from the posterior extremities, *mesonephric branches* from the mid-kidney and dorsal *intersegmental veins* from the body wall (Fig. 282 B). Median and ventral to the mesonephros are developed the *subcardinal veins*, which are connected at intervals with the posterior cardinal veins by mesonephric sinusoids, and with each other by anastomoses ventral to the aorta. Thus all the blood from the mesonephroi, posterior extremities, and dorsal body wall is in early stages drained by the posterior cardinal veins alone.

The development of the unpaired *vena cava inferior* begins when communication is established between the *right hepatic vein* of the liver and the *right subcardinal vein* of the mesonephros, primarily a tributary of the posterior cardinal vein (Lewis, 1902).

The liver on the right side becomes attached to the dorsal body wall, and from its point of union a ridge, the *plica venæ cavæ* (Fig. 199), extends caudalward. According to Davis (1910), capillaries from the subcardinal vein invade the *plica venæ cavæ*, and, growing cranially, meet and fuse with capillaries extending caudad from the liver sinusoids. Thus is formed the *vein of the plica venæ cavæ* (*x*, Fig. 282 A), which is already present in human embryos of 2.6 mm. (Kollmann). This vein rapidly enlarges, as also do the sinusoidal connections between the subcardinals and posterior cardinals at one point. Thus the blood from both lower posterior cardinals is now carried to the heart, chiefly by way of the right subcardinal and right hepatic veins (Fig. 282 B).

Soon, the posterior cardinals, just cranial to their enlarged anastomoses with the subcardinals, become small and are interrupted (Fig. 282 C). Cranial to their interruption, these veins atrophy and are replaced by the thoracic portions of new vessels, the *supracardinal veins*, which lie dorso-mesial to the posterior cardinals and extend on each side from the common cardinal veins to the union of the primitive iliac vessels. The new veins communicate in the thoracic region by a cross anastomosis and become the *azygos* and *hemiazygos* of the adult. The more caudal portions of the posterior cardinal veins likewise atrophy and are also replaced by the supracardinal vessels of the lumbar region (Fig. 282 C).

The blood from the lower trunk and leg region is now drained by the unpaired *inferior vena cava*, which is composed of the following veins: (1)

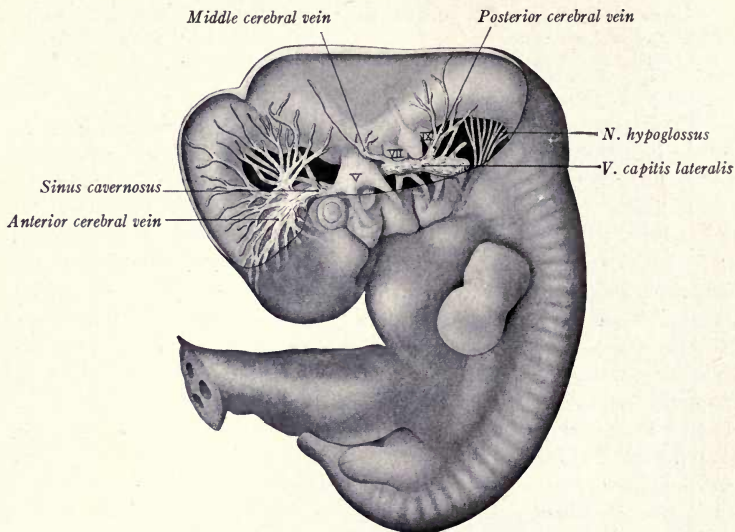


FIG. 283.—Veins of the head of a 9 mm. human embryo (after Mall). $\times 9$.

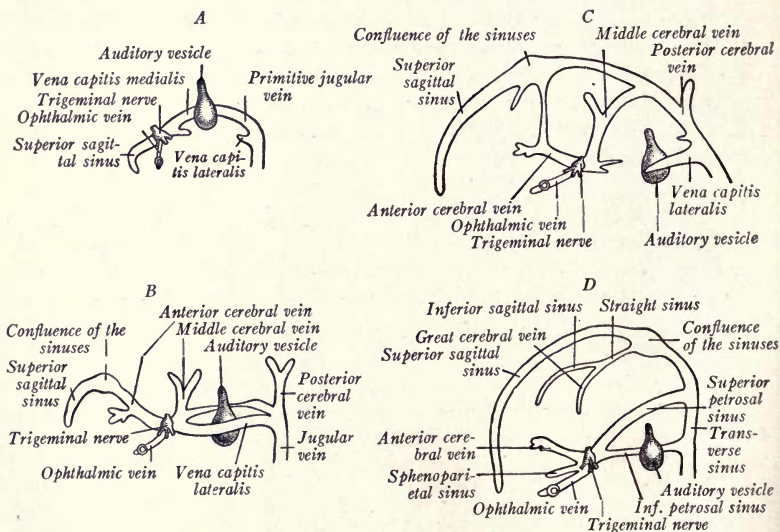


FIG. 284.—Four diagrams showing the development of the veins of the head (after Mall). A, At four weeks; B, at five weeks; C, at the beginning of the third month; D, from an older fetus.

the common hepatic and right hepatic veins (primitive right vitelline); (2) the vein of the plica venæ cavæ; (3) an inter-renal portion of the right subcardinal vein with its great mesial anastomosis; (4) the right supracardinal vein, below the level of the kidneys.

The permanent kidneys take up their positions opposite the great anastomosis between the subcardinals, and at this point the *renal veins* are developed (Fig. 282 B); the longer left renal vein differs from the right in that proximally it represents a left portion of the anastomosis itself (Fig. 282 D). A cephalic portion of the left subcardinal vein persists as the *left suprarenal vein*, which thus opens into the left renal instead of joining the inferior vena cava as does the *right suprarenal vein* of similar origin. The *left spermatic* or *ovarian vein* early drains into the left caudal border of the great subcardinal anastomosis, which, as we have seen, contributes to the left renal vein. The *right spermatic* or *ovarian vein* opens into the right border of that portion of the subcardinal anastomosis which is incorporated into the inferior vena cava. Thus the subcardinal veins aid in the formation of the inferior vena cava and the spermatic or ovarian vessels, whereas they constitute all of the suprarenal veins; the rest of the subcardinal system atrophies.

The *lumbar* veins develop from the same right supracardinal plexus that gives rise to the caudal segment of the inferior vena cava. Caudal to its lowest transverse connection with its mate (z, Fig. 282C), the right subcardinal vessel becomes the *right common iliac vein*. The corresponding portion of the similar left vein, plus the transverse anastomosis, becomes the *left common iliac vein*. The *external* and *internal* (hypogastric) *iliacs* persist after the posterior cardinal veins disappear and now join the new common iliacs.

Veins of the Extremities.—The primitive capillary plexus of the upper and lower limb buds gives rise to a *border vein* (Figs. 285 and 322), which courses about the periphery of the flattened limb buds (Hochstetter). In the upper extremity, the ulnar portion of the border vein persists, forming at different points the *subclavian*, *axillary*, *brachial*, and *basilic veins*. The border vein at first opens into the dorsal wall of the posterior cardinal vein (embryos of 10 mm.), but, as the heart shifts its position caudalward, it finally drains by a ventral connection into the anterior cardinal, or internal jugular vein (Lewis). The *cephalic vein* develops secondarily in connection with the ulnar border vein; later, in embryos of 23 mm., it anastomoses with the external jugular and finally drains into the axillary vein, as in the adult. With the development of the digits, the *vv. cephalica* and *basilica* become distinct, as in embryo of 35 mm., but later are again connected by a plexus on the dorsum mani, as in the adult (Evans).

In the *lower extremity*, the fibular portion of the primitive border vein persists. Later, the *v. saphena magna* arises separately from the posterior cardinal, gives off the *vv. femoralis* and *tibialis posterior*, and annexes the fibular border vein at the level of the knee. Distal to this junction the border vein persists as the *v. tibialis anterior*, and, probably, the *v. saphena parva*; proximally, it becomes greatly reduced, forming the *v. glutea inferior*.

Anomalies.—Anomalous blood vessels are of common occurrence. They may be due: (1) to the choice of unusual paths in the primitive vascular plexuses; (2) to the persistence of vessels usually obliterated, e. g., double superior or inferior venæ cavæ; right aortic arch; permanent ductus arteriosus; (3) to incomplete development, e. g., double aortæ.

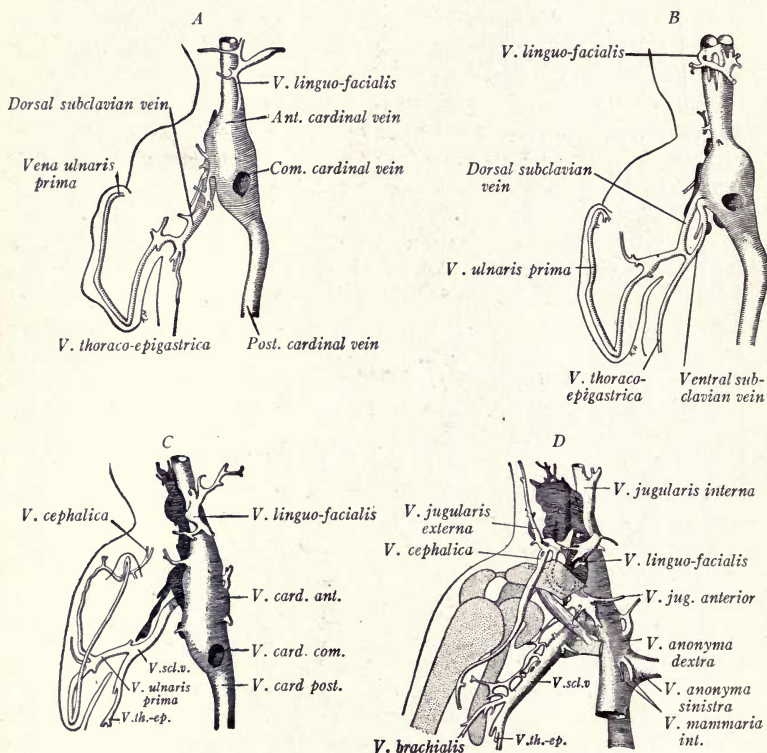


FIG. 285.—Four reconstructions of the veins of the human right arm (after F. T. Lewis). × about 15. A, 10 mm. embryo; B, 11.5 mm. embryo; C, 16 mm. embryo; D, 22.8 mm. embryo.

THE FETAL CIRCULATION AND CHANGES AT BIRTH

During fetal life oxygenated placental blood enters the embryo by way of the large *umbilical vein* and is conveyed to the liver (Fig. 286). There it mingles with the small amount of venous blood brought in by the *portal vein*. Thence it is carried to the inferior vena cava either directly, through the *ductus venosus*, or indirectly through the liver sinusoids and hepatic vein. The impure blood of the inferior vena cava and portal vein

affects but slightly the greater volume of pure placental blood. Entering the right atrium, it mingles somewhat with the venous blood returned through the superior vena cava. It is said that the blood from the inferior vena cava is directed by the valve of this vein through the *foramen ovale* into the left atrium (following the path of the sounds in Figs. 262

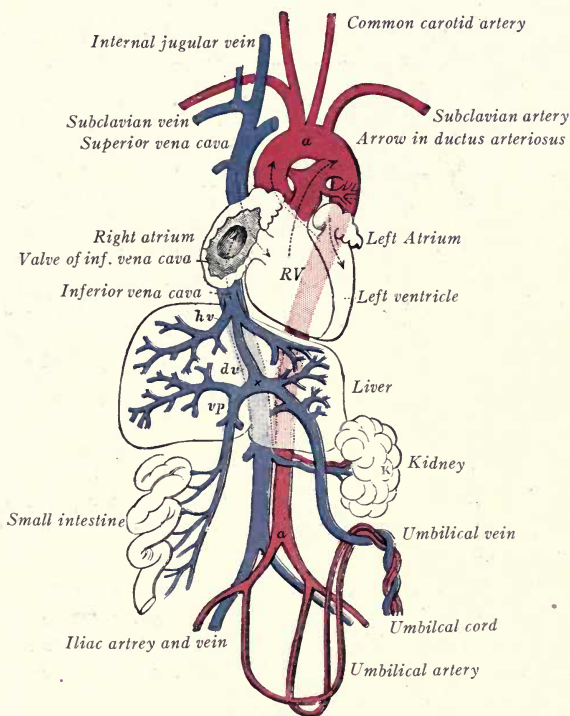


FIG. 286.—Diagrammatic outline of the organs of circulation in the fetus of six months (Allen Thomson). The arteries are conventionally colored red and the veins blue, irrespective of the nature of the blood conveyed by them. Arrows show the course of blood through the heart. *a*, Aortic arch; *dv*, ductus venosus, *hv*, hepatic vein, *vp*, portal vein.

to 264), which, before birth, receives little venous blood from the lungs. This purer blood of the left atrium enters the left ventricle, and is driven out through the aorta, to be distributed chiefly to the head and upper extremities.

The venous blood of the superior vena cava, slightly mixed, is supposed to pass from the right atrium into the right ventricle, whence it

passes out by the pulmonary artery. A small amount of this blood is conveyed to the lungs by the pulmonary arteries, but, as the fetal lungs do not function, most of it enters the dorsal aorta by way of the *ductus arteriosus*. Since the ductus is caudal to the origin of the subclavian and carotid arteries, its less pure blood is distributed to the trunk, viscera, and lower extremities. The placental circuit is completed by the *hypogastric*, or *umbilical arteries* by way of the umbilical cord.

Pohlman (Anat. Rec., vol. 2, 1908) interprets his experiments to indicate that, contrary to the generally accepted view, there is a mingling of the blood which enters the right atrium through the two caval veins. If this occurs, there would be no difference in the quality of blood distributed to the various parts of the body.

Changes at Birth.—At birth the placental circulation ceases and the lungs become functional. The *umbilical arteries* and *veins*, no longer used, contract and their lumina are obliterated by the thickening of the inner coat (tunica intima). The lumen of the umbilical artery is said to be occluded after four days, that of the umbilical vein within a week. The cord-like vein is persistent as the *ligamentum teres* of the liver; the arteries become the *obliterated hypogastrics*.

The *ductus venosus* atrophies because after birth only the blood from the portal vein enters the liver, and this is all drained into the liver sinuoids, forming the *portal circulation*. The ductus venosus is obliterated within two months and becomes the fibrous *ligamentum venosum*, embedded in the wall of the liver.

The *ductus arteriosus* ceases to function after birth, as all the blood from the pulmonary arterial trunk is conveyed to the expanded lungs. In most cases the ductus becomes impervious within four months after birth and persists as a solid, fibrous cord, the *ligamentum arteriosum*.

After birth, the large amount of blood now returned to the left atrium from the functional lungs equalizes the pressure in the two atria (p. 256). As a result, both during diastole and systole, the *septum primum*, or valve of the foramen ovale, is pressed against the *septum secundum*, closing the foramen ovale. Eventually, the two septa fuse—in one-third of all cases within three months, in two-thirds by the tenth year (p. 259).

THE LYMPHATIC SYSTEM

The lymphatic system originates in a plexus of lymphatic capillaries distributed along the primitive main venous trunks. By the dilation and coalescence of this network at definite regions five *lymph sacs* appear (Fig. 287). Paired *jugular sacs* arise in 10 to 11 mm. embryos, lateral to the internal jugular veins. In embryos of 23 mm. the unpaired *retroperitoneal sac* develops at the root of the mesentery, adjacent to the supra-

renal bodies, and the *cisterna chyli* also appears. Paired *posterior sacs* arise in relation to the sciatic veins in embryos 24 mm. long. These sacs at first contain blood which they soon discharge into neighboring veins, thereupon losing their venous connections. With relation to the lymph sacs as centers, the *thoracic duct* (at 30 mm.) and the *peripheral lymphatics*

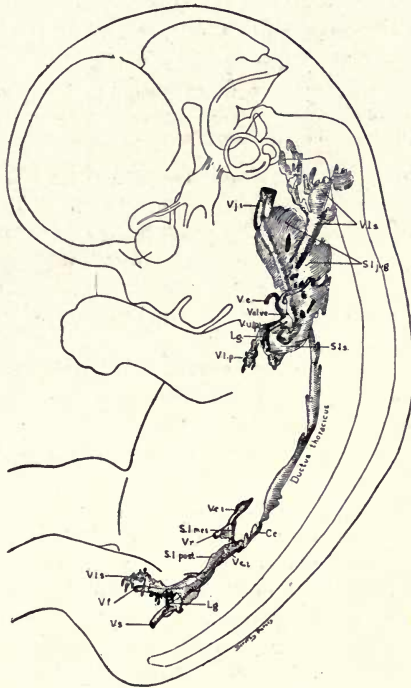


FIG. 287.—Flat reconstruction of the primitive lymphatic system in a human embryo 30 mm. long (Sabin). \times about 3.5. *C.c.*, Cisterna chyli; *Lg.*, lymph gland; *Sl.jug.*, jugular lymph sac; *Sl.mes.*, retroperitoneal lymph sac; *Sl.p.*, posterior lymph sac; *Sl.s.*, subclavian lymph sac; *V.c.*, cephalic vein; *V.c.i.*, inferior vena cava; *V.f.*, femoral vein; *V.j.i.*, internal jugular vein; *V.l.p.*, deep lymphatics; *V.l.s.*, superficial lymphatics; *V.r.*, renal vein; *V.s.*, sciatic vein; *V.u.(p.)* primitive ulnar vein.

develop. The jugular sacs alone acquire with the internal jugular veins secondary connections that are later utilized by the thoracic and right lymphatic ducts. The various sacs themselves are eventually transformed into chains of lymph nodes.

Two discordant views exist as to the exact mode of origin and growth of the lymphatics. According to Sabin (1909; 1916) and Lewis (1906),

sprouts, arising from the endothelium of veins, form the single and paired sacs already described. From these five sacs the thoracic duct and peripheral lymphatics develop chiefly as *endothelial outgrowths*. Thus, lymphatic vessels grow to the head, neck, and arm from the jugular sacs; to the hip, back, and leg from the posterior sacs; and to the mesentery from the retroperitoneal sac.

Other investigators (Huntington, 1911; 1914; McClure 1915) hold that the lymph sacs are formed *in situ* by the fusion of discrete mesenchymal spaces which become lined with an endothelium of transformed, bordering mesenchymal cells. Venous connections are purely secondary. The thoracic duct and the peripheral vessels develop similarly by the progressive fusion of separate clefts; hence, *endothelium can differentiate continually from young mesenchyma*. The further growth of endothelium already formed, is not denied. This general doctrine of the local origin of endothelium is unquestionably correct (cf. p. 247).

Lymph Glands.—Paired lymph glands appear during the third month, first in the axillary, iliac, and maxillary regions. Those from the lymph sacs develop later. Plexuses of lymphatics first form, either as ordinary networks of peripheral vessels, or as secondary networks produced by a connective-tissue invasion of the primitive lymph sacs. In either case, a capillary plexus, with simple connective-tissue septa, marks the first stage of development. Next (Fig. 288 A), lymphocytes collect in the connective tissue, forming *cortical nodules* which become associated with blood capillaries and later acquire *germinal centers*. Finally, the lymphoid tissue is channeled by sinuses formed from lymphatic capillaries. The *peripheral sinus* develops afferent and efferent vessels. The *central sinuses* cut the lymphoid tissue into *medullary cords*. In the larger lymph glands (Fig. 288 B) the connective tissue forms a definite *capsule* from which *trabeculae* dip into the gland.

Hæmal (Hæmolymph) Glands.—Their origin is traced by Meyer (1917) to condensations of mesenchyme which develop in relation to blood vessels, not lymphatics. The peripheral sinus arises independently; its vascular connections are secondary.

The Spleen.—This appears in embryos of about 10 mm. as a swelling on the left side of the dorsal mesogastrium near the dorsal pancreas (Fig. 289 A). The thickening is due to a temporary proliferation and invasion of mesothelial cells into the underlying mesenchyme, which, meanwhile, has also undergone local enlargement and vascularization. It is said that these cells from the peritoneal epithelium give rise to a large part, at least, of the future spleen. The splenic anlage becomes pinched off from the mesogastrium (Fig. 289 B) with which it is ultimately joined by a narrow band only.

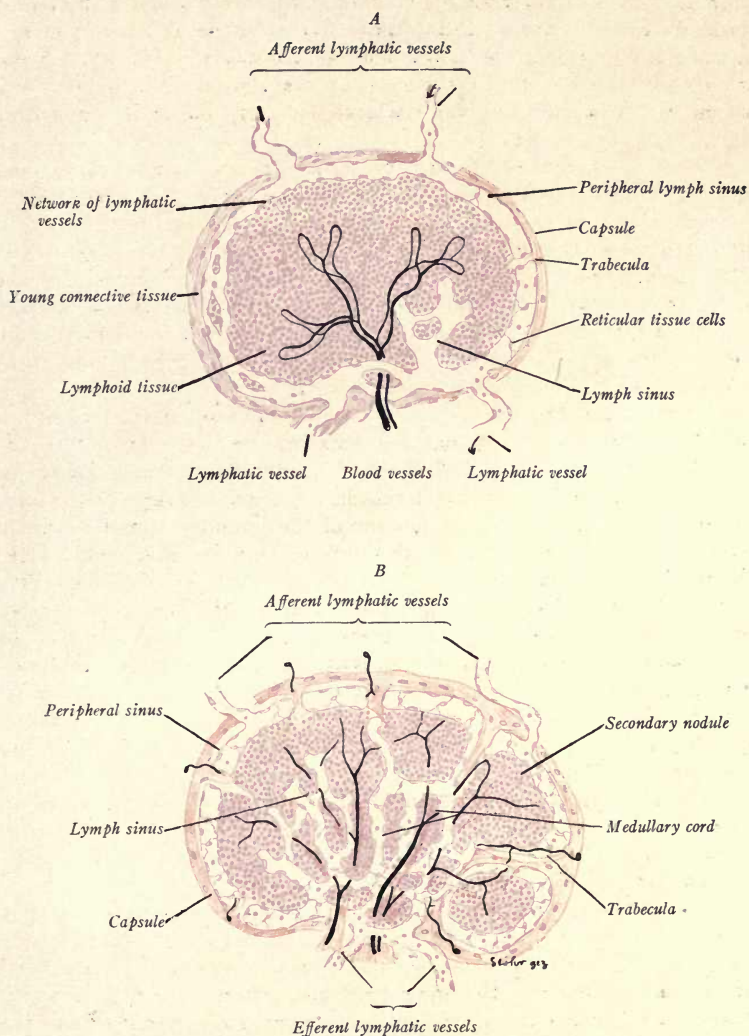
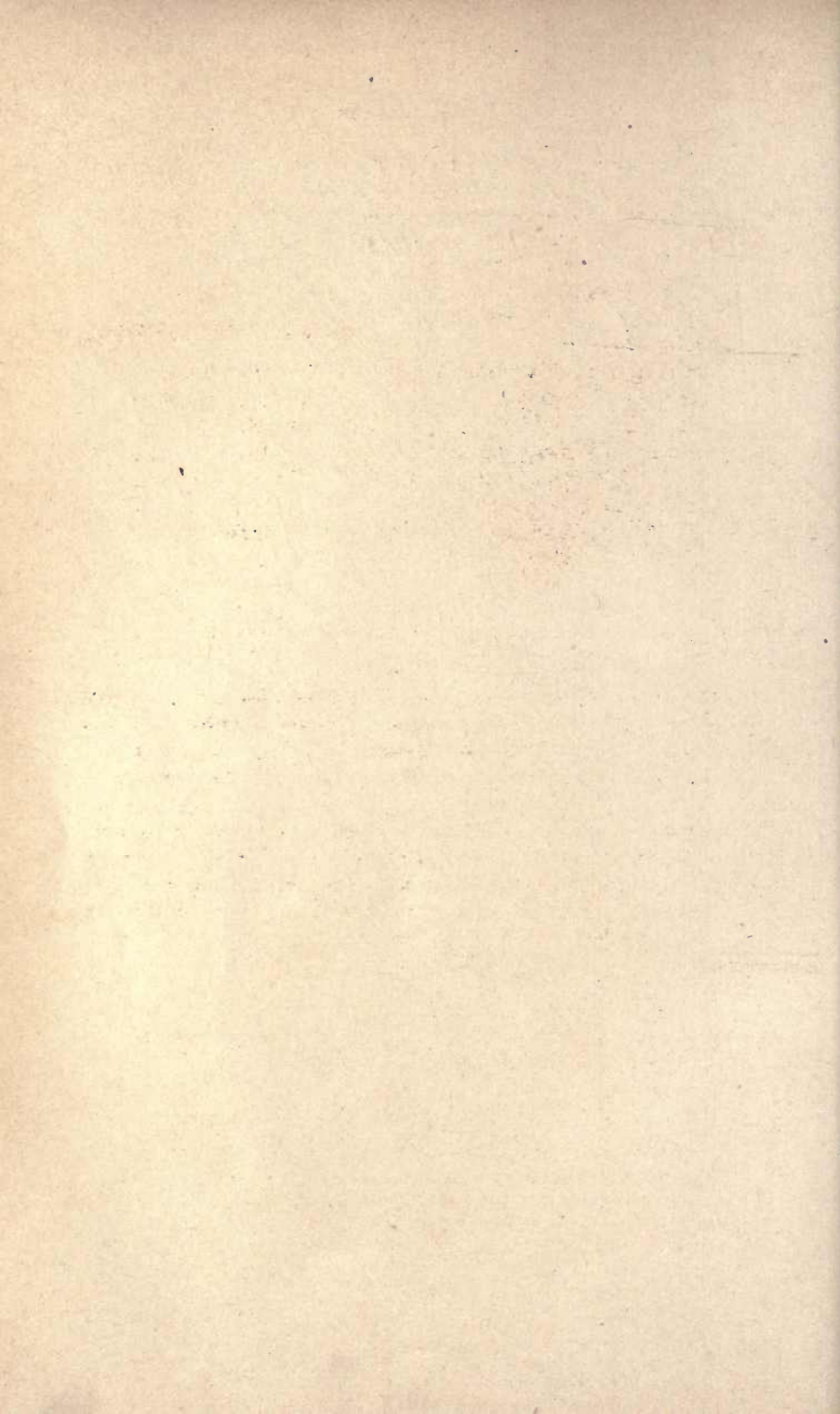


FIG. 288.—Diagrams representing four stages in the development of lymph glands. The earlier stages are shown on the left side of each figure (Lewis and Stöhr).



At first the blood vessels constitute a closed system. The peculiar adult circulation is acquired relatively late. Lifschitz has shown that, in human fetuses between 150 and 300 mm. long, red blood cells are actively formed in the splenic pulp as clusters around the giant cells.

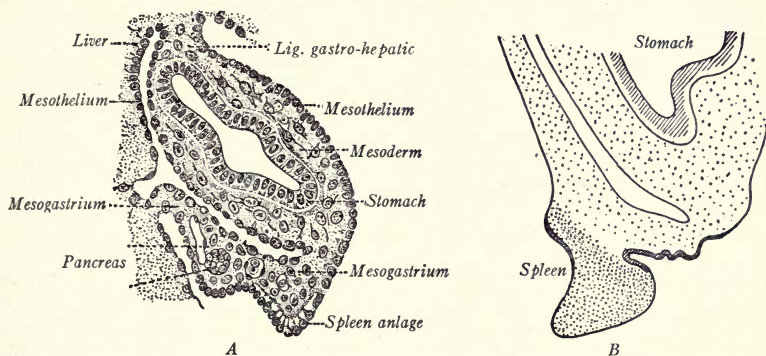


FIG. 289.—Two stages in the early development of the human spleen (dorsal is below). *A*, from an embryo of 10.5 mm. (Kollmann); *B*, from a 20 mm. embryo (Tonkoff).

The *lymphoid tissue* of the spleen first appears as *ellipsoids* about the smallest arteries in fetuses of four months. At seven months, the ovoid *splenic corpuscles* form as lymphoid nodules about the larger arteries. The *capsule*, *trabeculae* and *reticulum* differentiate from the cells of the common anlage.

The Glomus Coccygeum.—The coccygeal gland is present in 150 mm. (CH) fetuses as an encapsulated cluster of polyhedral cells at the apex of the coccyx. Later it becomes lobulated by the ingrowth of connective-tissue trabeculae and receives a rich vascular supply. According to Stoerck (1906), its tissue at no time resembles the chromaffin bodies, as is often stated.

CHAPTER X

HISTOGENESIS

THE primitive cells of the embryo are alike in structure. The protoplasm of each exhibits the fundamental properties of irritability, contractility, reproduction, and metabolism (the absorption, digestion, and assimilation of nutritive substances and the excretion of waste products, processes through which growth and reproduction are made possible). As development proceeds, there is a gradual differentiation of the cells into *tissues*, each tissue being composed of like cells, the structure of which has been adapted to the performance of a certain special function. In other words, there is division of labor and adaptation of cell structure to the function which each cell performs. The differentiation of tissue cells from the primitive cells of the embryo is known as *histogenesis*. On page 56 the derivatives of the germ layers were given. We shall now take up briefly the histogenesis of the tissues derived from the *entoderm*, *mesoderm*, and *ectoderm*.

HISTOGENESIS OF THE ENTODERMAL EPITHELIUM

The cells of the entoderm are little modified from their primitive structure. From the first they are concerned with the processes of absorption, digestion, assimilation, and excretion. They form always epithelial layers, lining the digestive and respiratory canals, and the glandular derivatives of these. In the pharynx, esophagus, and trachea the cells are early of columnar form and ciliated. The epithelium of the pharynx and esophagus becomes stratified and the surface layers flatten to form squamous cells. The stratified epithelium is developed from a basal germinal layer like the epidermis of the integument (see p. 294). Throughout the rest of the digestive canal the simple columnar epithelium of the embryo persists. At the free ends of the majority of the cells a cuticular membrane develops. Other cells are converted into unicellular mucous glands, or *goblet cells*. As outgrowths of the intestinal epithelium, are developed the simple tubular glands of the stomach and intestine, and the liver and pancreas.

In the respiratory tract, the entoderm forms at first a simple columnar epithelium. Later, in the trachea and bronchi this is differentiated into a pseudostratified, ciliated epithelium. The columnar epithelium of the

alveoli and alveolar ducts of the lungs is converted into the flattened respiratory epithelium.

The development of the thymus and thyreoid glands, liver and pancreas may be found in Chapter VII.

HISTOGENESIS OF THE MESODERMAL TISSUES

The differentiation of the mesoderm has been described on p. 53 ff. It gives rise to the mesodermal segments, intermediate cell masses, somatic and splanchnic layers, all of which are epithelia, and to the diffuse *mesenchyme*. The somatic and splanchnic layers of the mesoderm form on their coelomic surfaces a single layer of squamous cells, termed the *mesothelium*.

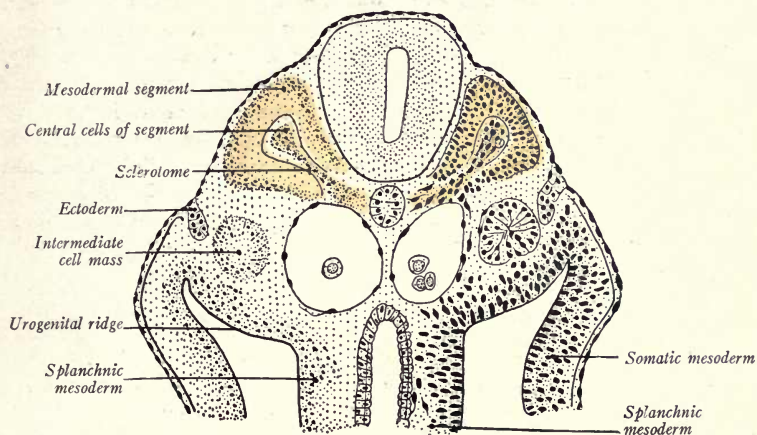


FIG. 290.—Transverse section of a 4.5 mm. human embryo, showing the development of the sclerotomes (Kollmann). \times about 300.

This is the covering layer of the pericardium, pleuræ, peritoneum, mesenteries, serous layer of the viscera, and lining the of vaginal sac in the scrotum. From this mesothelium is derived the spleen and also the epithelia of the genital glands and the Müllerian ducts.

The intermediate cell masses, or nephrotomes, are the anlagen of the pronephros, mesonephros, metanephros, and their ducts (p. 196).

The Sclerotomes and Mesenchyme.—The cavities of the mesodermal segments become filled with diffuse, spindle-shaped cells, derived from the adjacent walls; their median walls are next converted into similar tissue and the whole migrates mesially towards the neural tube and notochord, and eventually surrounds these structures (Figs. 290 and 323). This diffuse tissue is *mesenchyme* (see p. 55), and that derived from a single

mesodermal segment constitutes a *sclerotome*. The sclerotomes ultimately are converted into connective tissue, vertebræ, and the basal portion of the cranium. The persisting lateral plate of the mesodermal segment becomes a *dermo-myotome*, from which the voluntary muscle is differentiated, and, probably, the corium of the integument.

In the head region, cranial to the otocysts, no mesodermal segments are formed, but the primitive mesoderm is converted directly into mesenchyme. Mesenchyme is derived also from the somatic and splanchnic mesoderm and from the primitive-streak tissue. From the mesenchyme a number of tissues are developed (see p. 56). The origin of the blood and primitive blood vessels and lymphatics has been described (Chapter IX); it remains to trace the development of the supporting tissues and muscle fibers.

THE SUPPORTING TISSUES

The supporting tissues are peculiar in that a fibrous, hyaline, or calcified matrix is formed during their development from the mesenchyme, and this becomes greater in amount than the persisting cellular elements of the tissue.

CONNECTIVE TISSUE

Different views are held as to the differentiation of connective-tissue fibers. According to Laguess and Merkel, the fibers arise in an *inter-cellular matrix*, derived from the cytoplasm of mesenchymal cells. Szily holds that fibers are first formed as processes of epithelial cells and that into this fibrous network mesenchymal cells later migrate. The view generally accepted, that of Fleming, Mall, Spalteholz, and Meves, is that the primitive connective-tissue fibers are developed as parts of the cell, that is, are *intracellular* in origin.

The mesenchyme is at first compact, the cell nuclei predominating. Soon a syncytium is developed, the cytoplasm increasing in amount and forming an open network. Next, the cytoplasm is differentiated into a perinuclear, granular *endoplasm* and an outer, distinct, hyaline layer of *ectoplasm* (Fig. 291 A) (Mall, 1902). In the ectoplasm fibrils appear, apparently not mitochondrial in origin (M. R. Lewis, 1918).

Reticular Tissue.—Fine fibers arise in the ectoplasm of the mesenchymal syncytium. The nuclei and endoplasm persist as clasping reticular cells. According to Mall, reticular fibers differ chemically from white connective-tissue fibers.

White Fibrous Connective Tissue.—The differentiation of this tissue may be divided into two stages: (1) a prefibrous stage, during which the ectoplasm is formed rapidly by the endoplasm of the cells, and fibrils

resembling those of reticular tissue appear in the ectoplasm (Fig. 291 A); (2) the anastomosing fibers take the form of parallel bundles and are converted, through a chemical change, into typical white fibers. The spindle-shaped cells are transformed into the connective-tissue cells characteristic of the adult. In *areolar tissue*, the bundles of white fibers are interwoven to form a meshwork; in *tendon* they are arranged in compact, parallel fascicles. The cells of the tendons are compressed between the bundles of fibers and this accounts for their peculiar form and arrangement.

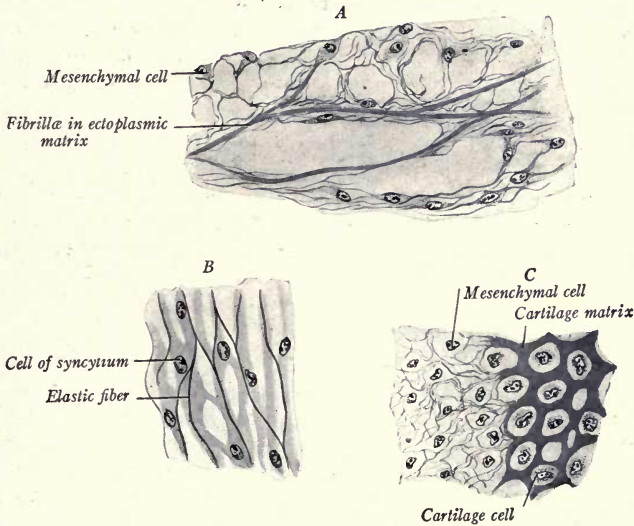


FIG. 291.—The differentiation of the supporting tissues (after Mall). $\times 270$. A, White fibers in the corium of a 5 cm. pig embryo; B, elastic fibers in the umbilical cord of a 7 cm. pig embryo; C, cartilage from the occipital bone of a 20 mm. pig embryo.

In the *cornea* of the eye, the cells retain their processes. The corneal tissue is thus embryonic in character and is without elastic fibers or blood vessels.

Elastic Tissue.—With the exception of the cornea and tendon, yellow elastic fibers develop in connection with all white fibrous connective tissue. Like the white fibers, they are produced in the ectoplasm of the mesenchymal syncytium (Fig. 291 B). They are developed as single fibers, but may coalesce to form the fenestrated membranes of the arteries. According to Ranvier, elastic fibers are produced by the union of ectoplasmic granules, but this view is not supported by either Mall or Spalteholz.

Adipose Tissue.—Certain of the mesenchymal cells give rise, not to fibroblasts, but to fat cells. They secrete within their cytoplasm droplets of fat which increase in size and become confluent (Fig. 292). Finally, a single fat globule fills the cell, and the nucleus and cytoplasm are pressed to the periphery. The fat cells are most numerous along the course of the blood vessels in areolar connective tissue and appear first during the fourth month.



FIG. 292.—Developing fat cells, the fat blackened with osmic acid (after Ranvier).

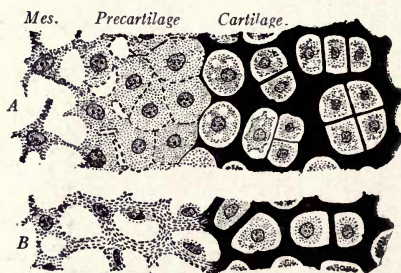


FIG. 293.—Diagrams of the development of cartilage from mesenchyma (Lewis and Stöhr). *A*, Based upon Studnicka's studies of fish; *B*, upon Mall's study of mammals. *Mes.*, mesenchyma.

CARTILAGE

Cartilage has been described as developing in two ways: (1) The mesenchymal cells increase in size and form a compact, cellular precartilage. Later, the hyaline matrix is developed between the cells from their cytoplasm (Fig. 293 *A*). The matrix may in this case be regarded as the ectoplasm of the cartilage cells. (2) According to Mall, mesenchymal cells give rise first to an ectoplasm in which fibrillae develop. Next, the cells increase in size and are gradually extruded until they lie in the spaces of the ectoplasmic matrix (Figs. 291 *C* and 293 *B*). Simultaneously, the ectoplasm undergoes both a chemical and structural change and is converted into the hyaline matrix peculiar to cartilage. About the cartilage cells the endoplasm produces capsules of hyaline substance.

The *interstitial growth* of cartilage is due: (1) to the proliferation of adult cartilage cells; (2) to the production of new matrix. *Appositional growth* also takes place, through the mitotic activity of the connective-tissue sheath, the *perichondrium*. Its inner cells are transformed into young cartilage cells.

In *hyaline cartilage*, the matrix remains hyaline. In *fibro-cartilage*, the fibrillations of the primitive ectoplasm are converted into white fibers. In *elastic cartilage*, yellow elastic fibers are formed in the hyaline matrix, according to Mall; before the hyaline matrix is differentiated, according to Spalteholz. Most of the bones of the skeleton are preformed in cartilage.

BONE

Bone is a tissue appearing relatively late in the embryo. There are developed two types: the *membrane bones* of the face and cranium, and the *cartilage bones* which replace the cartilaginous skeleton. The mode of histogenesis, however, is identical in both.

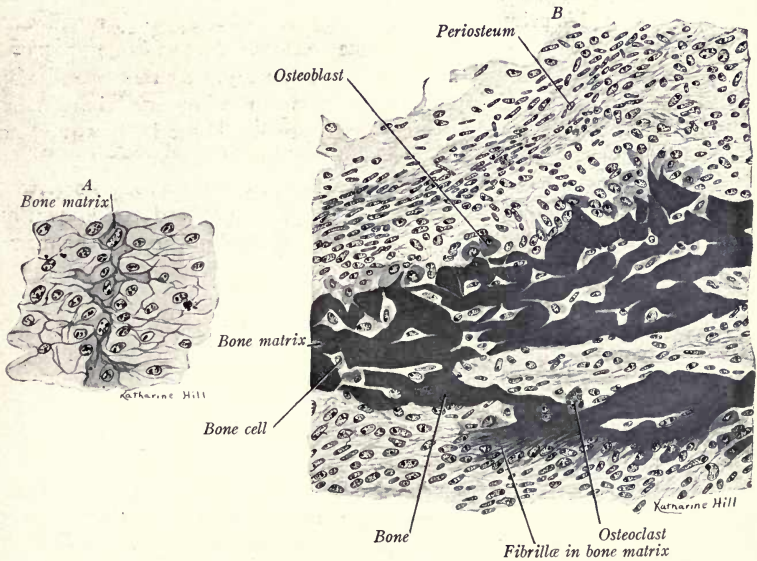


FIG. 294.—Two stages in the development of bone. *A*, Section through the frontal bone of a 20 mm. pig embryo (after Mall). $\times 270$. *B*, Section through the periosteum and bone lamellæ of the mandible of a 65 mm. human fetus. $\times 325$.

Membrane Bone.—The flat bones of the face and skull are not preformed as cartilage. The form of a membrane bone is determined by the development of a periosteal membrane from the mesenchyma. The bone matrix is differentiated within the *periosteum* from enlarged columnar cells, the *osteoblasts* (bone formers). Osteoblasts appear in clusters and from their cytoplasm is differentiated a fibrillated ectoplasmic matrix like that which precedes the formation of connective tissue and cartilage (Fig. 294 *A*). This fibrillated matrix, apparently by a chemical change,

is converted into a homogeneous bone matrix, which first takes the form of spicules. Others view the fibrillated matrix as an intercellular product and the bone matrix as an interfibrillar deposit. However this may be, the spicules coalesce, form a network of bony plates, and constitute the bone matrix upon the surface of which osteoblasts are arranged in a single layer like the cells of an epithelium (Fig. 294 *B*). As the matrix of the bone is laid down, osteoblasts become engulfed and form *bone cells*. The bone cells are lodged in spaces termed *lacunæ*. These are connected by microscopic canals, the *canaliculi*, in which delicate cell processes course.

Ossification begins at the middle of the bone and proceeds in all directions from this primary center. The plates of the spongy membrane bone are formed about blood vessels as centers. As the bone grows at the periphery, the bone matrix is resorbed centrally. At this time, large, multinucleate cells appear upon the surfaces of the bone matrix. These cells are known as *osteoclasts* (bone destroyers). There is, however, no positive evidence that the osteoclasts are active in dissolving the bone. They may be interpreted also as degenerating, fused osteoblasts (Arey, 1920). The cavities in which they are frequently lodged are known as *Howship's lacunæ*. The bone lamellæ of the central portion of the membrane bone are gradually resorbed, and this portion of the bone is of a spongy texture. Some time after birth, compact bone lamellæ are laid down by the osteoblast cells of the inner layer of the periosteum. In the case of flat bones, compact *inner* and *outer plates*, or *tables*, are thus developed with spongy bone between them. The spaces in the spongy bone are filled by derivatives of the mesenchyme: reticular tissue, blood vessels, fat cells, and developing blood cells. These together constitute the *red bone marrow*.

Cartilage Bone.—The form of the cartilage bone is determined by the preformed cartilage and its surrounding membrane, the perichondrium (Fig. 296). Bone tissue is developed as in membrane bones, save that the cartilage is first gradually destroyed and the new bone tissue develops: (1) in, and (2) about it. In the first case, the process is known as *endochondral* bone formation. In the second case, it is known as *perichondral*, or *periosteal* bone formation.

Endochondral Bone Formation.—The cartilage cells enlarge, become arranged in characteristic rows, and lime is provisionally deposited in the matrix (Fig. 295). The perichondrium becomes the periosteum. From its inner or osteogenic layer, which is densely cellular, ingrowths invade and resorb the cartilage and fill the primary marrow cavities. The invading osteogenic tissue gives rise to *osteoblasts* and *bone marrow*. The osteoblasts deposit bone directly upon persisting portions of the carti-



FIG. 295.—A longitudinal section of the two distal phalanges from the finger of a five-months' human fetus (Sobotta). $\times 15$. *Kn*, Cartilage showing calcification and resorption; *eK*, endochondral bone; *M*, marrow cavity; *pK*, periosteal bone.

lage. As new bone is developed peripherally, it is resorbed centrally to form large marrow spaces. Eventually, all of the cartilage matrix, and probably the cartilage cells as well, are destroyed.

Perichondral Ossification.—Compact bone is developed by the osteogenic layer of the periosteum, and thus are produced the *periosteal lamellæ*. In the ribs this is said to be the only method of ossification. Those bone lamellæ deposited about a blood vessel are concentrically arranged and form the *concentric lamellæ* of an *Haversian system*. The *Haversian canal* of adult bone is merely the space occupied by blood vessels. Between the Haversian systems are *interstitial lamellæ*.

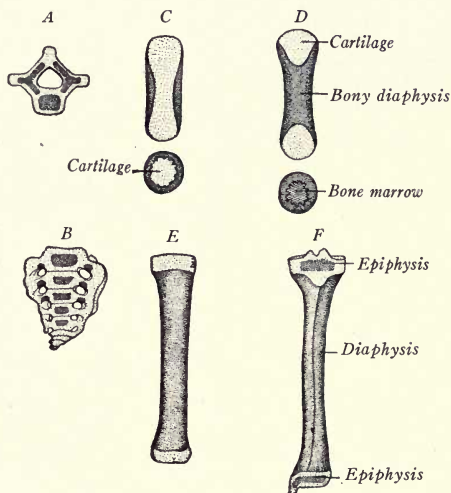


FIG. 296.—Diagrams to show the method of growth of: A, vertebra; B, sacrum; C-F, a long bone (tibia).

Growth of Cartilage Bones.—In cartilage bones there is no interstitial growth as in cartilage. Most of the cartilage bones have more than one center of ossification and growth is due to the expansion of the intervening cartilage. Flat bones grow at the periphery; ring like bones, such as the vertebræ, have three primary centers of ossification, between which the cartilage continues to grow (Fig. 296 A). In the case of the numerous long bones of the skeleton, the primitive ossification center forms the shaft, or *diaphysis* (Fig. 296 C-F). The cartilage at either end of the diaphysis grows rapidly and thus the bone increases in length. Eventually, osteogenic tissue invades these cartilages and new ossification centers, the *epiphyses*, are formed, one at either end. When the growth of the bone

in length is completed, the epiphyses, by the ossification of the intervening cartilage, are united to the diaphysis.

The shaft of the long bones grows in diameter by the peripheral deposition of bone lamellæ and the central resorption of the bone. In the larger long bones, spongy, or cancellated bone tissue persists at the ends, but in the middle portion a large *medullary*, or *marrow cavity* is developed. This is filled chiefly with fat cells and constitutes the *yellow bone marrow*.

Regeneration of Bone.—If bone is injured or fractured, new bone is developed by osteoblasts derived either from the periosteum or from the bone marrow. The repair of a fracture is usually preceded by the formation of cartilage which unites the ends of the bones and is later replaced by bone. In adults, the periosteum is regarded as especially important in the regeneration of bone tissue.

Joints.—In joints of the *synarthrosis* type, in which little movement is allowed, the mesenchyma between the ends of the bones differentiates into connective tissue or cartilage. This persists in the adult.

In joints of the *diarthrosis* type, the bones are freely movable. The mesenchyma between the bones develops into an open connective tissue in which a cleft appears, the *joint cavity*. The cells lining this cavity flatten out and form a more or less continuous layer of epithelium, the *synovial membrane*. From the connective tissue surrounding the joint cavity are developed the various fibrous ligaments typical of the different joints. Ligaments or tendons which apparently course through the adult joint cavities represent secondary invasions, covered with reflexed synovial membrane and hence really external to the cavity.

THE HISTOGENESIS OF MUSCLE

The muscular system is composed of muscle fibers; these form a tissue in which contractility has become the predominating function. The fibers are of three types: (1) *smooth muscle cells*, found principally in the walls of the viscera and blood vessels; (2) *striated skeletal muscle*, chiefly attached to the elements of the skeleton and producing voluntary movements; (3) *striated cardiac muscle*, forming the myocardium of the heart. All three types are derived from the mesoderm. The only exceptions are the smooth muscle of the iris, and the smooth muscle of the sweat glands, which are derived from the ectoderm.

Smooth Muscle.—Certain stellate cells of the mesenchyma enlarge, elongate, and their cytoplasm becomes more abundant. The resulting spindle-shaped cells remain attached to each other by cytoplasmic bridges and develop in the superficial layer of their cytoplasm coarse, non-contractile myoglia fibrils (Fig. 297), similar to the primitive fibrillæ of con-

nective tissue (McGill, 1907). The myoglia fibrils may extend from cell to cell, thus connecting them. These fibrils are the products of coalesced granules found within the cytoplasm of the myoblasts. In embryos of 30 mm. fine myofibrillæ are differentiated in the cytoplasm of the myoblasts and give it a longitudinally striated appearance. The cytoplasmic processes of the muscle cells, the cytoplasmic bridges, later give rise to white



FIG. 297.—Two stages in the development of smooth muscle fibers (after McGill). *A*, from the esophagus of a 13 mm. pig ($\times 550$); coalescing granules give rise to coarse myoglia fibrils. *B*, from the esophagus of a 27 mm. pig ($\times 850$); both coarse myoglia fibrils and fine myofibrils are present.

connective-tissue fibers which envelop the muscle fibers and bind them together. Smooth muscle also increases in amount by mitotic division and the transformation of interstitial connective-tissue cells.

Striated Skeletal Muscle.—All striated voluntary muscle is derived from the mesoderm, either from the myotomes of the segments (muscles of

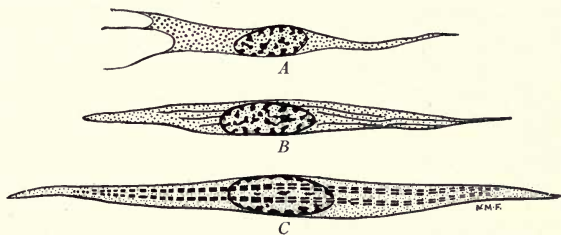


FIG. 298.—Stages in the histogenesis of skeletal muscle (after Godlewski). *A*, myoblast a 13 mm. sheep embryo; *B*, myogenous myofibrils in a myoblast of a 10 mm. guinea pig embryo; *C*, myoblast with longitudinally splitting striated myofibrils from an 8.5 mm. rabbit embryo.

the trunk) or from the mesenchyma (muscles of the head). According to Bardeen (1910), after the formation of the sclerotome (Fig. 290), which gives rise to skeletal tissue, the remaining portion of the primitive segment constitutes the *myotome*; all of its cells become myoblasts. On the contrary Williams (1910), finds that in the chick only the cells of the dorsal and mesial walls of a mesodermal segment are myoblasts. By

multiplication they form a mesial *myotome*, while the lateral cells of the original mesodermal segment persist as a *dermatome* and give rise only to the connective tissue of the corium (Fig. 223). The dermatome lies lateral to the myotome (Fig. 47) and the two together constitute the *dermo-myotome*.

As to the manner of origin of the individual muscle fibers, there is also a difference of opinion. It is generally believed that the myoblasts elongate, and, by the repeated mitotic division of their nuclei, become multinucleated. Godlewski, (1902), however, holds that several myoblasts unite to form a single muscle fiber. The nuclei lie at first centrally, surrounded by the granular sarcoplasm (Fig. 298 A). The sarcoplasmic granules become arranged in rows and constitute the *myofibrillæ*, which increase in number by longitudinal splitting (Fig. 298 B, C). The myofibrillæ soon differentiate alternating dark and light bands, due to differences in density, and the individual fibrillæ, become so grouped that their dark and light bands coincide (Fig. 298 C). During development, the muscle fibers increase enormously in size, the nuclei migrate to the surface, and the myofibrillæ are arranged in bundles, or *muscle columns* (sarcostyles). The fibrils of each column are said to arise by the longitudinal splitting of single, primitive myofibrils.

While smooth muscle forms a syncytium and the enveloping connective-tissue fibers are developed directly from the muscle cells, in the case of striated skeletal muscle each fiber is a multinucleated entity which is bound to others by connective tissue of independent origin.

According to Baldwin (1912), the nucleus and perinuclear sarcoplasm is separated from the rest of the muscle fiber by the sarcolemma. With Apathy (1888), he would therefore regard the myofibrillæ as a differentiated product of the muscle cells, to be homologized with connective-tissue fibers. There is little to support this view.

During the later stages in the development of striated voluntary muscle there is, according to many observers, an active degeneration of the muscle fibers.

Striated Cardiac Muscle.—This is developed from the splanchnic mesoderm that forms both the epicardium and the myocardium (Fig. 255). The cells of the myocardium at first form a syncytium in which myofibrillæ develop from the linear union of cytoplasmic granules. The myofibrillæ are developed at the periphery of the syncytial strands of cytoplasm and extend long distances in the syncytium. They multiply rapidly and form dark and light bands, as in skeletal muscle. The syncytial character of cardiac muscle persists in the adult and the nuclei remain central in position. The *intercalated discs*, typical of adult cardiac muscle, probably appear in the early months of fetal life.

HISTOGENESIS OF THE ECTODERMAL DERIVATIVES

Besides forming the enamel of the teeth and the salivary glands (p. 153 ff), the ectoderm gives rise: (1) to the epidermis and its derivatives (subcutaneous glands, nails, hair, and the lens and conjunctiva of the eye); (2) to the nervous system and sensory epithelia; (3) to parts of certain glands producing internal secretions, such as the pituitary body, suprarenal glands, and chromaffin bodies.

We shall describe here the histogenesis of the epidermis, the development of its derivatives, and the histogenesis of the nervous tissues, reserving for final chapters the development of the nervous organs and the glands formed in part from them.

THE EPIDERMIS

The single-layered ectoderm of the early embryo, by the multiplication of its cells, becomes differentiated into a two-layered epidermis,

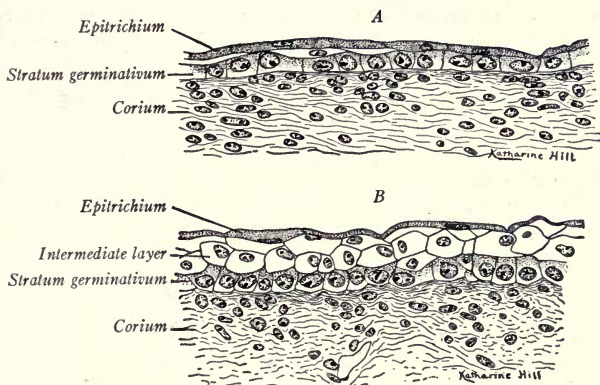


FIG. 299.—Sections of the integument from a 65 mm. human fetus. $\times 440$. A, From the neck, showing a two-layered epidermis and the beginning of a third intermediate layer; B, from the chin, with three well developed epidermal layers.

composed of an inner layer of cuboidal or columnar cells, the *stratum germinativum*, and an outer layer of flattened cells, the *epitrichium*, or *periderm* (Fig. 299 A).

The *stratum germinativum* is the reproducing layer of the epidermis. As development proceeds, its cells divide and gradually give rise to new layers above, until the epidermis becomes a many-layered, or *stratified epithelium*. The periderm is always the outermost layer of the epidermis. During the third and fourth months the epidermis is typically three-layered, the outer, flattened layer forming the periderm, a middle layer of polygonal cells, the intermediate layer, and the inner, columnar layer, the

stratum germinativum (Fig. 299 B). After the fourth month the epidermis becomes many layered. The inner layers of cells now form the *stratum germinativum* and are actively dividing cells, united with each other by cytoplasmic bridges. The outer layers of cells become cornified, the cornification of the cells proceeding from the stratum germinativum toward the surface. Thus, next the germinal layer, are cells containing *keratohyalin* which constitute the double-layered *stratum granulosum*. A thicker layer, above the stratum granulosum, shows cells in which drops of a substance called *eleidin* are formed. These droplets, supposed to represent softened keratohyalin, give these cells a clear appearance when examined unstained. Hence the layer is termed the *stratum lucidum*. In the outer layers of the epidermis the thickened walls of the cells become cornified and in the cells themselves a fatty substance collects. These layers of cells constitute the *stratum corneum*. Its cells are also greatly flattened, especially at the surface.

When the hairs develop they do not penetrate the outer periderm layer of the epidermis, but, as they grow out, lift it off (sixth month). Hence this layer is known also as the *epitrichium* (layer upon the hair). Desquamated epitrichial and epidermal cells mix with the secretion of the sebaceous glands to form the pasty *vernix caseosa* that smears the fetal skin. Pigment granules appear soon after birth in the cells of the stratum germinativum. These granules are probably formed *in situ*. Negro children are quite light in color at birth, but within six weeks their integument has reached the definitive degree of pigmentation.

The *derma*, or *corium*, of the integument is developed from mesenchyme, perhaps from definite dermatomes (Fig. 323) of the mesodermal segments (p. 292). At about the end of the third month a differentiation into the compact corium proper and the areolar subcutaneous tissue occurs. From the corium, *papillæ* project into the stratum germinativum.

Anomalies.—The deposition of pigment in the epidermis and elsewhere may fail (*albinism*), or be over abundant (*melanism*). The defects of pigmentation sometimes affect local areas only. *Naevi* are either pigmented spots ('*moles*'), or purple discolorations ('*birthmarks*') caused by cavernous vascular plexuses in the corium. *Ichthyosis* results from an excessive thickening of the stratum corneum. In severe cases, horny plates 5 mm. thick are formed; these are separated by deep cracks. *Dermoid cysts* (p. 218) resulting from epidermal inclusions, are not infrequent along the lines of fusion of embryonic structures, e. g., branchial grooves, mid-dorsal and mid-ventral body wall.

THE HAIR

Hairs are derived from thickenings of the epidermis and begin to develop at the end of the second month on the eyebrows, upper lip, and chin. The hair of the general body integument appears at the beginning of the fourth month.

The first evidence of a hair anlage is the elongation of a cluster of epidermal cells in the inner germinal layer (Fig. 300 A). The bases of these cells project into the corium, and, above them, cells of the epidermis are arranged parallel to the surface. The elongated cells continue to grow downward until a cylindrical hair anlage is produced (Fig. 300 B, C). This consists of an outer wall, formed of a single layer of columnar cells, continuous with the basal layer of the epidermis. This wall bounds a central mass of irregularly polyhedral epidermal cells. About the hair anlage the mesenchyma forms a sheath, and at its base a condensation of mesenchyme produced the anlage of the *hair papilla*, which projects into



FIG. 300.—Section through the integument of the face of a 65 mm. human fetus, showing three stages in the early development of the hair. $\times 330$.

the enlarged base of the hair anlage. As development proceeds, the hair anlage grows deeper into the corium and its base enlarges to form the *hair bulb* (Fig. 300 C). The hair differentiates from the based epidermal cells surrounding the hair papilla. These cells give rise to a central core which grows toward the surface, distinct from the peripheral cells which form the *outer sheath* of the hair (Fig. 301). The central core of cells becomes the *inner hair sheath* and the *shaft* of the hair. Two swellings of the outer hair sheath appear on the lower side of the obliquely directed hair anlage. The more superficial of these is the anlage of the *sebaceous gland* (Fig. 301). The deeper swelling is the *epithelial bed*, a region where the cells by rapid division contribute to the growth of the hair follicle.

Superficial to the bulb, the cells of the hair shaft become cornified and differentiated into an outer *cuticle*, middle *cortex*, and central inconstant *medulla*. The hair grows at the base and is pushed out through the

central cavity of the anlage, the cells of which degenerate. When the hair projects above the surface of the epidermis it breaks and carries with it the *epitrichial layer*. The mesenchymal tissue which surrounds the hair follicle in the neighborhood of the epithelial bed gives rise to the smooth fibers of the *arrector pili muscle*. Pigment granules develop in the basal cells of the hair and give it its characteristic color.

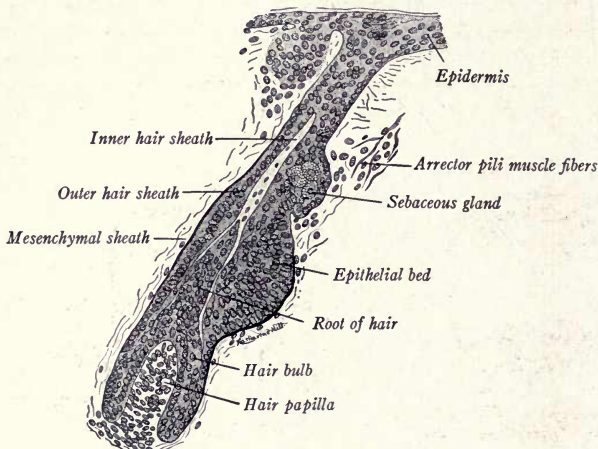


FIG. 301.—Longitudinal section through a developing hair from a five and one-half months' human fetus (after Stöhr). $\times 220$.

The first generation of 'lanugo' hairs are short-lived, all except those covering the face being cast off soon after birth. The coarser, replacing hairs develop, at least in part, from new follicles. Thereafter, hair is shed periodically throughout life.

Anomalies.—*Hypertrichosis* refers to excessive hairiness which may be general or local, as in the exhibited 'hairy monsters.' In the rare *hypotrichosis*, the congenital absence of hair is usually associated with defective teeth and nails.

SWEAT GLANDS

The sudoriparous, or sweat glands begin to develop in the fourth month from the epidermis of the finger tips, the palms of the hands, and the soles of the feet. They are formed as solid downgrowths from the epidermis, but differ from hair anlagen in having no mesenchymal papillæ at their bases. During the sixth month the tubular anlagen of the gland begin to coil, and, in the seventh month, their lumina appear. The inner layer of cells forms the *gland cells*, while the outer cells become transformed into *smooth muscle fibers* which here arise from the ectoderm. In the axillary region, sweat glands occur which are large and branched.

MAMMARY GLANDS

The tubular mammary glands are peculiar to mammals. In embryos of 9 mm. (Figs. 94 and 118) an ectodermal thickening extends ventro-laterally between the bases of the limb buds on either side. This linear epidermal thickening is the *milk line*. In the future pectoral region of this line, by the thickening and downgrowth of the epidermis, there is formed the papilla-like anlage of the mammary gland (Fig. 302 A). From this epithelial anlage buds appear (B) which elongate and form solid cords, 15 to 20 in number, the anlagen of the *milk ducts* (C). These branch in the mesenchymal tissue of the corium and eventually produce the alveolar

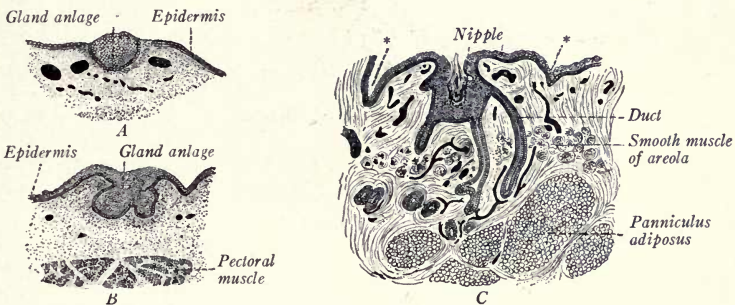


FIG. 302.—Sections representing three stages in the development of the human mammary gland (Tourneux). A, fetus of 32 mm.; B, of 102 mm.; C, of 244 mm. *, Groove limiting glandular area.

end pieces of the mammary glands. In the region where the milk ducts open on the surface the epidermis is evaginated to form the *nipple*. The glands yield a little secretion ('witch milk') at birth; they enlarge rapidly at puberty and are further augmented during pregnancy, while two or three days after parturition they become functionally active.

The mammary glands are regarded as modified sweat glands. This homology is made because their development is similar, and because in the lower mammals their structure is the same. Rudimentary mammary glands (of Montgomery), which also resemble sweat glands, occur in the areola about the nipple. In many mammals, numerous pairs of mammary glands are developed along the milk line (pig, dog, etc.); in some a pair of glands is developed in the pectoral region (primates, elephants); in others, glands are confined to the inguinal region (sheep, cow, horse).

Anomalies.—Supernumerary mammary glands (*hypermastia*) or nipples (*hyperthelia*) are not infrequent between the axilla and groin. These represent independent differentiations along the primitive milk line.

THE NAILS

The anlages of the nails proper are derived from the epidermis and may be recognized in fetuses of 45 mm. (CR). A nail anlage forms on the dorsum of each digit and extends from the tip of the digit almost to the articulation of the terminal phalanx. At the base of the anlage, that is, proximally, the epidermis is folded inward to form the proximal *nail fold* (posterior nail fold of the adult) (Fig. 303 C). The nail fold also extends laterally on either side of the nail anlage and forms the *lateral nail fold* of the adult (A, B).

The material of the nail is developed in the lower layer of the proximal nail fold (C). In certain of the epidermal cells, which, according to

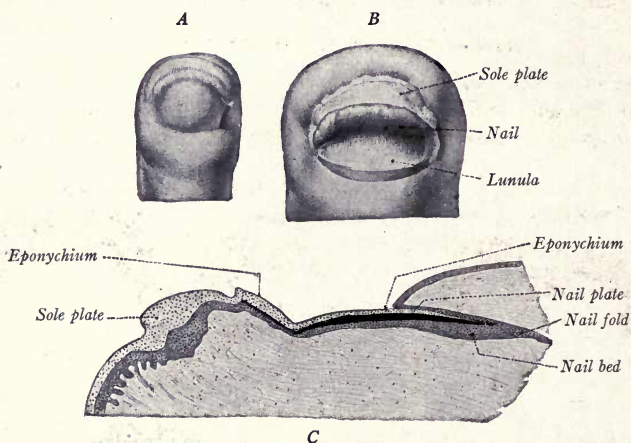


FIG. 303.—Figures showing the development of the nail. A, From a 40 mm. human fetus ($\times 20$); B, from a 100 mm. fetus ($\times 13$); C, longitudinal section from a 100 mm. fetus ($\times 24$). (Kollmann.)

Bowen, represent a modified stratum lucidum, there are developed keratin, or horn fibrils during the fifth month of fetal life. These appear without the previous formation of keratohyalin granules, as is the case in the cornification of the stratum corneum. The cells flatten and form the plate-like structure of which the solid substance of the nail is composed. Thus the nail substance is formed in the proximal nail fold as far distad as the outer edge of the *lunula* (the whitish crescent at the base of the adult nail). The underlying epidermis, distal to the lunula, takes no part in the development of the nail substance. The corium throws its surface of contact with the nail into parallel longitudinal folds that produce the longitudinal ridges of the nail. The nail is pushed toward the tip of the

digit by the development of new nail substance in the region of the nail fold. The stratum corneum and the epitrichium of the epidermis for a time completely cover the nail matrix and are termed the *eponychium* (Fig. 303 C). Later, this is thrown off, but a portion of the stratum corneum persists during life as the curved fold of epidermis which adheres to the base of the adult nail. During life the nail constantly grows at its base (proximally), is shifted distally over the nail bed, and projects at the tip of the digit.

The nails of man are the homologues of the claws and hoofs of other mammals. During the third month thickenings of the integument over the distal ends of the metacarpals and metatarsals become prominent. These correspond to the *touch-pads* on the feet of clawed mammals. Similar pads are developed on the under sides of the distal phalanges.

HISTOGENESIS OF THE NERVOUS TISSUES

The primitive anlage of the nervous system consists of the thickened layer of ectoderm along the mid-dorsal line of the embryo. This is the *neural plate* (Fig. 304 A, B) which is folded to form the *neural groove*

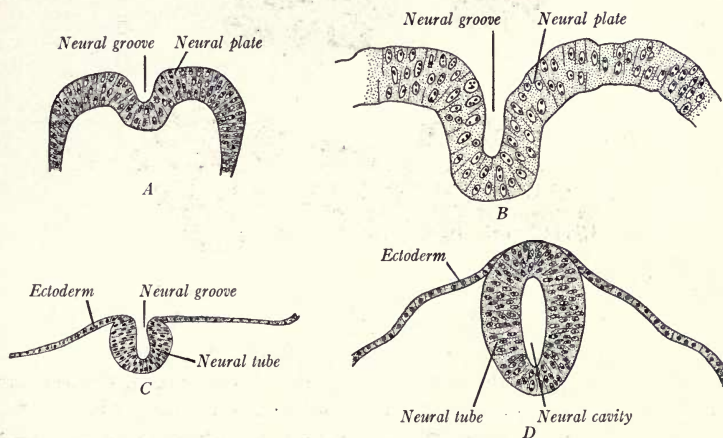


FIG. 304.—Four sections showing the development of the neural tube in human embryos. A, An early embryo (Keibel); B, at 2 mm. (Graf Spee); C, at 2 mm. (Mall); D, at 2.7 mm. (Kollmann).

(Figs. 77 A and 78). The edges of the neural plate come together and form the *neural tube* (Fig. 304 C, D). The cranial portion of this tube enlarges and is constricted into the three primary vesicles of the brain (Fig. 324). Its caudal portion remains tubular and constitutes the spinal cord. From the cells of this tube, and the ganglion crest connected with it, are differ-

entiated the nervous tissues, with the single exception of the nerve cells and fibers of the olfactory epithelium.

Differentiation of the Neural Tube.—The cells of the neural tube differentiate into two products. There are formed: (1) *nerve cells* and *fibers*, in which irritability and conductivity have become the predominant

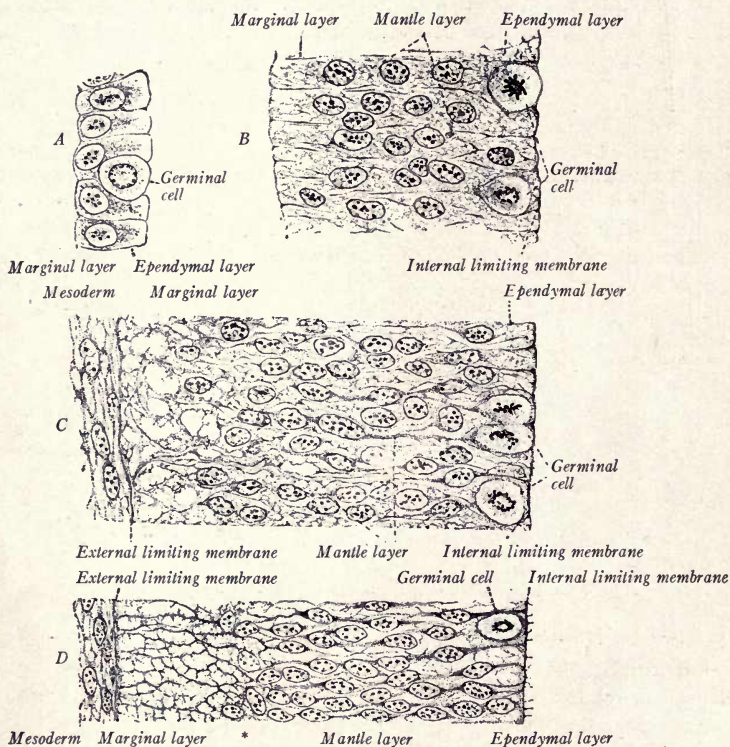


FIG. 305.—Three stages in the differentiation of the neural tube (after Hardesty). $\times 590$. A, From a rabbit embryo before the closure of the neural tube; B, from a 5 mm. pig embryo after closure; C, from a 7 mm. pig embryo; D, from a 10 mm. pig embryo. *, Boundary between mantle and marginal layers.

functions; (2) *neuroglia cells* and *fibers*, which constitute the supporting, or skeletal tissue, peculiar to the nervous system. The differentiation of these tissues has been studied by Hardesty (1904) in pig embryos. The wall of the neural tube, consisting at first of a single layer of columnar cells, becomes many-layered, and, finally, three zones are differentiated (Fig. 305 A-D). As the wall becomes many-layered the cells lose their

sharp outlines and form a compact, cellular syncytium which is bounded, on its outer and inner surfaces, by an *external* and *internal limiting membrane* (B). In a 10 mm. embryo the cellular strands of the syncytium are arranged radially and nearly parallel (D). The nuclei are now so grouped that there may be distinguished three layers: (1) an inner *ependymal zone*, with cells abutting on the internal limiting membrane, their processes extending peripherally; (2) a middle *mantle*, or *nuclear zone*, and (3) an outer, or *marginal zone*, non-cellular, into which nerve fibers grow. The ependymal zone contributes cells for the development of the mantle layer (D). The cellular mantle layer forms the gray substance of the central nervous system, while the fibrous marginal layer constitutes the white substance of the spinal cord.

The primitive *germinal cells* of the neural tube divide by mitosis and give rise to the *ependymal cells* of the ependymal zone and to *indifferent*

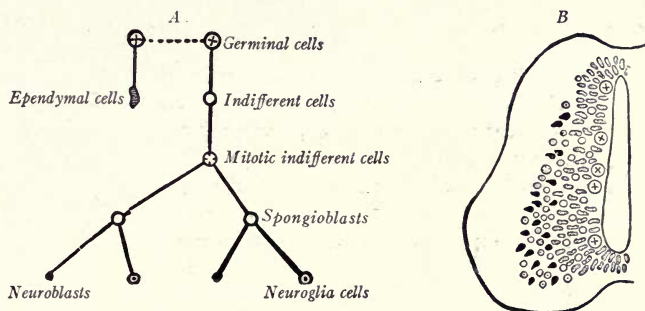


FIG. 306.—Diagrams showing the differentiation of the cells of the neural tube (after Schaper).

cells of the mantle layer. From these latter arise *spongioblasts* and *neuroblasts* (Fig. 306). The spongioblasts are transformed into *neuroglia cells* and *fibers*, which form the supporting tissue of the central nervous system; the neuroblasts are primitive nerve cells, which, by developing cell processes, are converted into *neurons*. The neurons are the structural units of the nervous tissue.

The Differentiation of Neuroblasts into Neurons.—The nerve fibers are developed as outgrowths from the neuroblasts, and a nerve cell with all its processes constitutes a *neuron* or cellular unit of the nervous system. The origin of the nerve fibers as processes of the neuroblasts is best seen in the development of the root fibers of the spinal nerves.

This *neuron concept* of the development of the nerve fibers is the one generally accepted at the present time. It assumes that all axons and dendrites are formed as outgrowths from nerve cells, an hypothesis first promulgated by His. The embryological evidence is

supported by experiment. It has long been known from the work of Waller that if nerves, are severed, the fibers distal to the point of section, and thus isolated from their nerve cells will degenerate; also, that regeneration will take place from the central stumps of cut nerves, the fibers of which are still connected with their cells. More recently Harrison (1906), experimenting on amphibian larvæ, has shown: (1) that no peripheral nerves develop if the neural tube and crest are removed; (2) that isolated ganglion cells growing in clotted lymph will give rise to long axon processes in the course of four or five hours.

A second theory, supported by Schwann, Balfour, Dohrn, and Bethe, assumes that the nerve fibers are in part differentiated from a chain of cells, so that the neuron would represent a multicellular, not a unicellular structure. Apáthy and Ö. Schulze modified this *cell-chain theory* by assuming that the nerve fibers differentiate in a syncytium which intervenes between the neural tube and the peripheral end organs. Held further modified this theory by assuming that the proximal portions of the nerve fibers are derived from the neuroblasts and ganglion cells and that these grow into a syncytium which by differentiation gives rise to the peripheral portion of the fiber.

Efferent Fibers of the Spinal Nerves.—At the end of the first month, clusters of neuroblasts separate themselves from the syncytium in the mantle layer of the neural tube. The neuroblasts become pear-shaped, and from the small end of the cell a slender primary process grows out (Figs. 307 and 308). This process becomes the *axon* or *axis cylinder*. The primary processes may course in the marginal layer of the neural tube, or, converging, may penetrate the marginal layer ventro-laterally and form the ventral roots of the spinal nerves. Similarly, the efferent fibers of the cerebral nerves grow out from neuroblasts of the brain wall. Within the cytoplasm of the nerve cells and their primary processes, strands of fine fibrils are early differentiated (Fig. 307 B). These, the *neurofibrillæ*, are usually assumed to be the conducting elements of the neurons. The cell bodies of the efferent neurons soon become multipolar by the development of branched secondary processes, the *dendrons* or *dendrites*.

Development of the Spinal Ganglia and Afferent Neurons.—After the formation of the neural plate and groove, a longitudinal ridge of cells appears on each side where the ectoderm and neural plate are continuous (Fig. 309 A). This ridge of ectodermal cells is the *neural*, or *ganglion crest*. When the neural tube is formed and the ectoderm separates from it, the cells of the ganglion crest overlie the neural tube dorso-laterally (Fig. 309 C). As development continues they separate into right and left linear crests, distinct from the neural tube, and migrate ventro-laterally to a position between the neural tube and myotomes. In this position the ganglion crest forms a band of cells extending the whole length of the spinal cord and as far cephalad as the otic vesicles. At regular intervals in its course along the spinal cord the proliferating cells of the crest give rise to enlargements, the *spinal ganglia* (Fig. 358). The spinal ganglia are arranged segmentally and are connected at first by

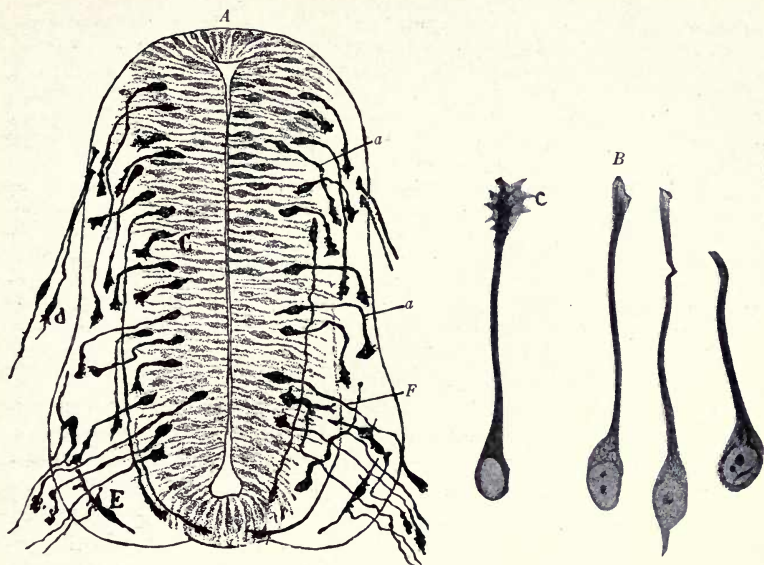


FIG. 307.—The differentiation of neuroblasts in chick embryos of the third day. *A*, Transverse section through the spinal cord, showing neuraxons (*F*) growing from neuroblasts and from bipolar ganglion cells (*d*). *B*, Single neuroblasts, showing neurofibrils and incremental cone (*c*). Cajal.

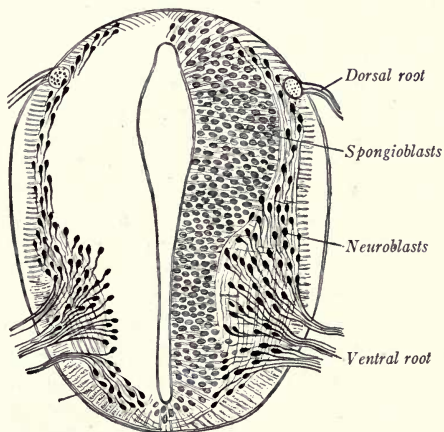


FIG. 308.—Transverse section of the spinal cord from a human fetus of five weeks, showing the origin of ventral root fibers from neuroblasts (His in Marshall) 150. \times .

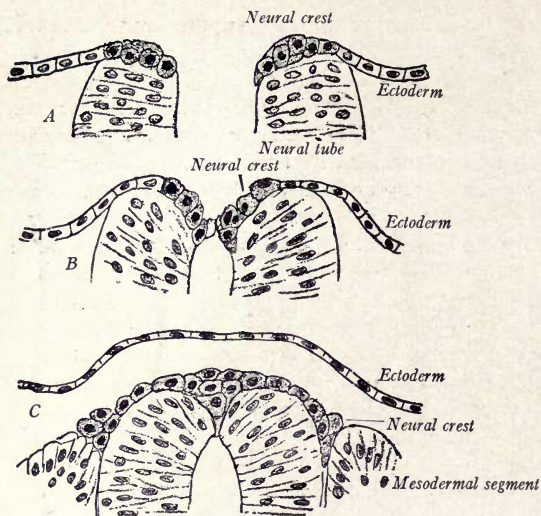


FIG. 309.—Three stages in the development of the ganglion crest in human embryos (after von Lenhossek in Cajal).

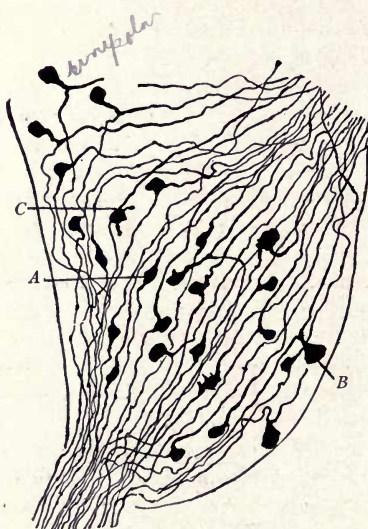


FIG. 310.—Stages in the formation of unipolar ganglion cells (Cajal). From a 44 mm. human fetus.

bridges of cells that later disappear. In the hind-brain region, certain ganglia of the cerebral nerves develop from the crest but are not segmentally arranged.

The cells of the spinal ganglia differentiate into: (1) *ganglion cells*, and (2) *supporting cells*, groups which are comparable to the neuroblasts and spongioblasts of the neural tube. The neuroblasts of the ganglia become fusiform and develop a primary process at either pole; thus these neurons are of the bipolar type (Fig. 307, *d*). The centrally directed processes of the ganglion cells converge, and, by elongation, form the dorsal roots. They penetrate the dorso-lateral wall of the neural tube, bifurcate, and course cranially and caudally in the marginal layer of the spinal cord. By means of branched processes they come in contact with the neurons of the mantle layer. The peripheral processes of the ganglion cells, as the *dorsal spinal roots*, join the ventral roots, and together with them, constitute the *trunks* of the spinal nerves (Fig. 325).

At first bipolar, (Fig. 310, *A*), the majority of the ganglion cells become unipolar, either by the fusion of the two primary processes or by the bifurcation of a single process. The process of the unipolar ganglion is now T-shaped. Many of the bipolar ganglion cells persist in the adult, while others develop several secondary processes and thus become multipolar in form. In addition to forming the spinal ganglion cells, neuroblasts of the ganglion crest are believed to migrate ventrally and form the *sympathetic ganglia* (Fig. 325).

Differentiation of the Supporting Cells of the Ganglia.—The supporting cells of the spinal ganglia at first form a syncytium in the meshes of which are found the neuroblasts. They differentiate: (1) into flattened *capsule cells*, which form capsules about the ganglion cells; and (2) into *sheath cells*, which ensheath the axon processes of both dorsal and ventral root fibers and are continuous with the capsules of the ganglion. It is probable that many of the sheath cells migrate peripherally along with the developing nerve fibers (Harrison). They are at first spindle-shaped, and, as primary sheaths, enclose bundles of nerve fibers. Later, by the proliferation of the sheath cells, the bundles are separated into single fibers, each with its sheath (of Schwann), or *neurilemma*. Each sheath cell forms a segment of the neurilemma, the limits of contiguous sheath cells being indicated by constrictions, the *nodes of Ranvier*.

The Myelin Sheath.—During the fourth month an inner *myelin*, or *medullary sheath* appears about many nerve fibers. This consists of a spongy framework of *neurokeratin* in the interstices of which a fatty substance, *myelin*, is deposited. The origin of the myelin sheath is in doubt. By some (Ranvier) it is believed to be a differentiation of the neurilemma, the myelin being deposited in the substance of the nucleated sheath cell.

By others (Kölliker, Bardeen) the myelin is regarded as a direct or indirect product of the axis cylinder. Its integrity is dependent at least upon the nerve cell and axis cylinder, for, when a nerve is cut, the myelin very soon shows degenerative changes.

In the central nervous system there is no distinct neurilemma sheath investing the fibers. Sheath cells are said to be present and most numerous during the period when myelin is developed. Hardesty derives the sheath cells in the central nervous system of the pig from a portion of the supporting cells, or *spongioblasts*, of the neural tube, and finds that these cells give rise to the myelin of the fibers.

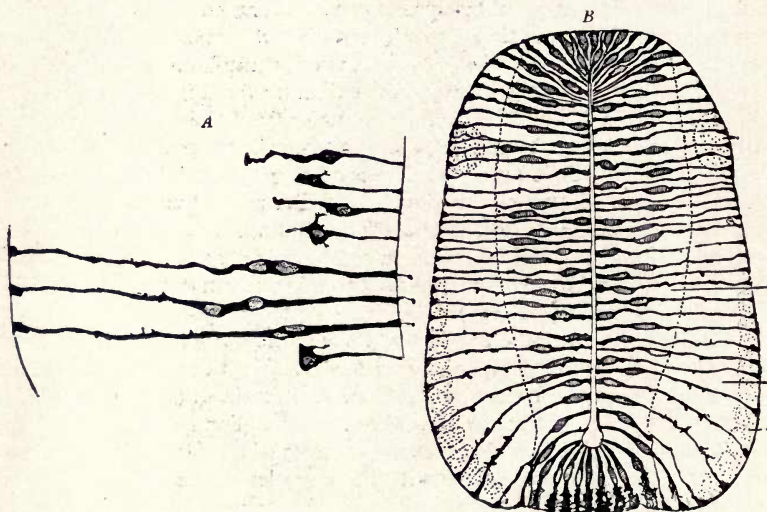


FIG. 311.—Ependymal cells from the embryonic neural tube. A, Chick embryo of first day; B, of third day. (Cajal).

Those fibers which are first functional receive their myelin sheaths first. The myelination of nerve fibers is only completed between the second and third year (Westphal). Many of the peripheral fibers, especially those of the sympathetic system, remain *unmyelinated* and supplied only with a neurilemma sheath. The myelinated fibers, those with a myelin sheath, have a glistening white appearance and give the characteristic color to the *white substance* of the central nervous system and to the peripheral nerves. Ranson (1911) has shown that large numbers of unmyelinated fibers also occur in the peripheral nerves and spinal cord of adult

mammals and man. Those found in the spinal nerves arise from the small cells of the spinal ganglia.

Development of the Supporting Cells of the Neural Tube.—The spongioblasts of the neural tube (p. 301) differentiate into the supporting tissue of the central nervous system. This includes the *ependymal cells* which line the neural cavity, and form one of the primary layers of the neural tube, and *neuroglia cells* and their *fibers*.

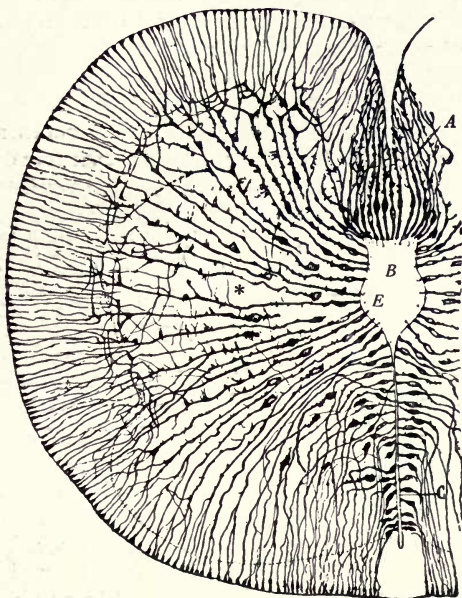


FIG. 312.—Ependymal cells of the lumbar cord from a human fetus of 44 mm. (Cajal). A, Floor plate; B, central canal; C, line of future fusion of neural walls; E, ependymal cells; *, neuroglia cells and fibers.

We have described how the strands of the syncytium formed by the spongioblasts become arranged radially in the neural tube of early embryos (Fig. 305 D). As the wall of the neural tube thickens, the strands elongate *pari passu* and form a radiating branched framework (Fig. 311). The group of spongioblasts which line the neural cavity constitute the *ependymal layer*. Processes from these cells radiate and extend through the whole thickness of the neural tube to its periphery. The cell bodies are columnar and persist as the lining of the central canal and ventricles of the spinal cord and brain (Fig. 312).

Near the median line of the spinal cord, both dorsally and ventrally, the supporting tissue retains its primitive ependymal structure in the adult. Elsewhere, the supporting framework is differentiated into *neuroglia cells* and *fibers*. The neuroglia cells form part of the spongioblastic syncytium and are scattered through the mantle and marginal layers of the neural tube. By proliferation they increase in number and their form depends upon the pressure of the nerve cells and fibers which develop around them.

Neuroglia fibers are differentiated (in a manner comparable to the formation of connective-tissue fibers, Fig. 291) from the cytoplasm and cytoplasmic processes of the neuroglia cells, and, as the latter primarily form a syncytium, the neuroglia fibers may extend from cell to cell. The neuroglia fibers develop late in fetal life and undergo a chemical transformation into *neurokeratin*, the same substance that is found in the sheaths of myelinated fibers.

CHAPTER XI

THE MORPHOGENESIS OF THE SKELETON AND MUSCLES

I. THE SKELETAL SYSTEM

THE skeleton comprises: (1) the axial skeleton (skull, vertebræ, ribs, and sternum) and (2) the appendicular skeleton (pectoral and pelvic girdles and the limb bones). Except for the flat bones of the face and skull, which develop directly in membrane, the bones of the skeleton exhibit first a blastemal, or membranous stage, next a cartilaginous stage, and finally a permanent, osseous stage.

For a detailed account of the development of the various bones of the skeleton the student is referred to Bardeen, Keibel and Mall, vol. 1.

THE AXIAL SKELETON

The primitive axial skeleton of all vertebrates is the *notochord*, or *chorda dorsalis*, the origin of which has been traced on pp. 34 and 36. The notochord constitutes the only skeleton of *Amphioxus*, whereas in fishes and amphibians it is replaced in part, and in higher animals almost entirely, by the permanent *axial skeleton*. In the development of mammals, this transient elastic rod disappears early, except in the intervertebral discs where it persists as the *nuclei pulposi*.

The Vertebræ and Ribs.—The mesenchyme derived from the sclerotomes grows mesad (Figs. 290 and 323) and comes to lie in paired segmental masses on either side of the notochord, separated from similar masses before and behind by the *intersegmental arteries*. In embryos of about 4 mm., each sclerotome soon differentiates into a caudal, compact portion and a cranial, less dense half (Fig. 313 A). From the caudal portions, horizontal tissue masses now grow toward the median line and enclose the notochord, thus establishing the *body* of each vertebra. Similarly, dorsal extensions form the *vertebral arch*, and ventro-lateral outgrowths, the *costal processes*. The looser issue of the cranial halves also grows mesad and fills in the intervals between successive denser regions.

The denser caudal half of each sclerotomic mass presently unites with the less dense cranial half of the sclerotome next caudad to form the an-

lages of the definitive *vertebræ* (Fig. 313 *B*). Mesenchymal tissue, filling the new intervertebral fissure thus formed, gives rise to the *intervertebral discs*. Since a vertebra is formed from parts of two adjacent sclerotomes, it is evident that the intersegmental artery must now pass over the body of a vertebra, and the myotomes and *vertebræ* alternate in position.

Following this *blastemal* stage, centers of *chondrification* appear, two centers in the vertebral body, one in each half of the vertebral arch, and one in each costal process. These centers enlarge and fuse to form a cartilaginous vertebra; the union of the costal processes, which will give rise to ribs, with the body is, however, temporary, an articulation forming

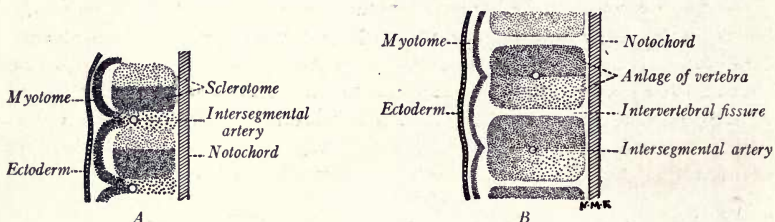


FIG. 313.—Frontal sections through the mesodermal segments of the left side of human embryos. *A*, at about 4 mm., showing the differentiation of the sclerotomes into less dense and denser regions; *B*, at about 5 mm., illustrating the union of the halves of successive sclerotomes to form the anlagen of the *vertebræ*.

later. *Transverse* and *articular processes* grow out from the vertebral arch, and the rib cartilages, having in the meantime formed *tubercles*, articulate with the transverse processes somewhat later. The various *ligaments* of the vertebral column arise from mesenchyme surrounding the *vertebræ*.

Finally, at the end of the eighth week, the stage of *ossification* sets in. A single center appears in the body, one in each half of the arch, and one near the angle of each rib (Fig. 296*A*). The replacement of cartilage to form a solid mass is not completed until several years after birth. At about the seventeenth year, secondary centers appear in the cartilage still covering the cranial and caudal ends of the vertebral body and form the disc-like, bony *epiphyses*. These unite with the vertebra proper to constitute a single mass at about the twentieth year.

While the foregoing account holds for *vertebræ* in general, a few deviations occur. When the *atlas* is formed, a body differentiates as well, but it is appropriated by the body of the *epistropheus* (axis), thereby forming the tooth-like *dens* of the latter. The sacral and coccygeal *vertebræ* represent reduced types. At about the twenty-fifth year the sacral *vertebræ* unite to form a single bony mass, and a similar fusion occurs between the rudimentary coccygeal *vertebræ*.

The *ribs*, originating as ventro-lateral outgrowths from the vertebral bodies, reach their highest development in the thoracic region. In the cervical region they are short; their tubercles fuse with the transverse processes and their heads with the vertebral bodies, thus leaving intervals, the *transverse foramina*, through which the vertebral vessels course. In the lumbar region the ribs are again diminutive and are fused to the transverse processes. The rudimentary ribs of the sacral vertebra are represented by flat plates which unite on each side to form a *pars ateralis* of the sacrum. With the exception of the first coccygeal vertebra, ribs are absent in the most caudal vertebræ.

The Sternum.—The sternal anlagen arise as paired mesenchymal bands, with which the first eight or nine thoracic ribs fuse secondarily (Whitehead and Waddell, 1911). After the heart descends into the thorax, these cartilaginous *sternal bars*, as they may now be termed, unite in a cranio-caudal direction to form the sternum, at the same time incorporating a smaller mesial sternal anlage (Fig. 314). Ultimately, one or two pairs of the most caudal ribs lose their sternal connections, the cor-

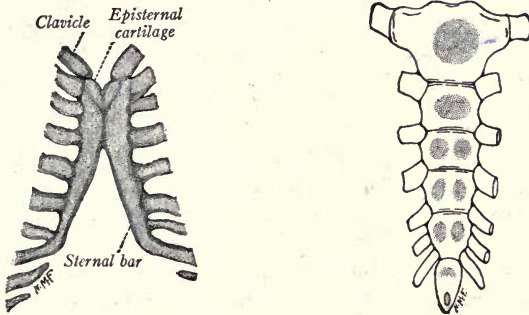


FIG. 314.—Formation of the sternum in a human fetus during the third month (modified after Ruge). FIG. 315.—Sternum of a child, showing centers of ossification.

responding portion of the sternum constituting the *xiphoid process* in part. At the cranial end of the sternum there are two imperfectly separated episternal cartilages with which the clavicles articulate. These usually unite with the longitudinal bars and contribute to the formation of the *manubrium*. Variations in the ossification centers are not uncommon, although a primitive, bilateral, segmental arrangement is evident (Fig. 315). In the two cranial segments, however, unpaired centers occur.

The Skull.—The earliest anlage of the skull consists in a mass of dense mesenchyme which envelops the cranial end of the notochord and extends cephalad into the nasal region. Laterally, it forms wings which enclose

the neural tube. Except in the occipital region, where there are indications of the incorporation into the skull of three or four vertebræ, the skull is from the first devoid of segmentation.

Chondrification begins in the future occipital and sphenoidal regions, in the median plane and extends cephalad and to a slight extent dorsad. At the same time the internal ear becomes invested with a cartilaginous *periotic capsule* which eventually unites with the occipital and sphenoidal cartilages (Fig. 316). The *chondrocranium* as it is termed is thus confined chiefly to the base of the skull, the bones of the sides, roof, and the face being of membranous origin. Chondrification also occurs more or less extensively in the branchial arches, and, as will appear presently, the first two pairs contribute substantially to the formation of the skull.

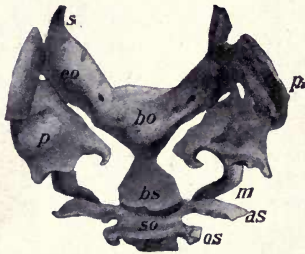


FIG. 316.—Reconstruction of the chondrocranium of a human embryo of 14 mm. (Levi in McMurrich). *as*, Alisphenoid; *bo*, basi-occipital; *bs*, basisphenoid; *eo*, exoccipital; *m*, Meckel's cartilage; *os*, orbitosphenoid; *p*, periotic; *ps*, presphenoid; *so*, sella turcica; *s*, supra-occipital.

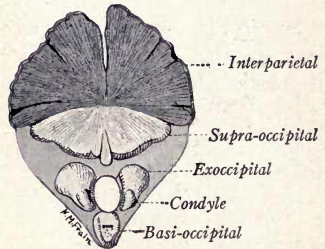


FIG. 317.—Occipital bone of a human fetus of four months (after Sappey). The portions still cartilaginous are shown as a homogeneous background.

In the period of *ossification*, which now ensues it becomes evident that some bones which are separate in adult lower animals fuse to form compound bones in the human skull. The sphenoid and temporal bones, for example, represent five primitive pairs each. As such components may arise either in membrane or cartilage, the compound nature of certain adult bones is explained.

Ossification of the Chondrocranium.—The Occipital Bone.—Ossification begins in the occipital region during the third month. Four centers appear at right angles about the foramen magnum (Fig. 317). From the ventral center arises the *basilar (basi-occipital)* part of the future bone; from the lateral centers the *lateral (exoccipital)* parts which bear the condyles; and from the dorsal, originally paired center, the *squamous (supra-occipital)* part below the superior nuchal line. The *squamous*

(*interparietal*) part above that line is an addition of intramembranous origin. These several components do not fuse completely until about the seventh year.

The Sphenoid Bone.—Ten principal centers arise in the cartilage that corresponds to this bone (Fig. 318): (1 and 2) in each *ala magna* (*alisphenoid*); (3 and 4) in each *ala parva* (*orbitosphenoid*); (5 and 6) in the *corpus* between the *alæ magnæ* (*basisphenoid*); (7 and 8) in each *lingula*; (9 and 10) in the *corpus* between the *alæ parvæ* (*presphenoid*). Intramembranous bone also enters into its composition forming the orbital, and temporal portion of each *ala magna* and the mesial laminae of each *pterygoid process* (except the hamulus). Fusion of the various parts is completed during the first year.

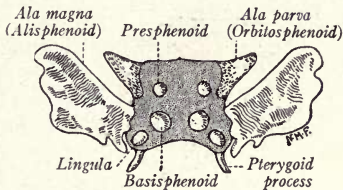


FIG. 318.—Sphenoid bone of a human fetus of nearly four months (after Sappey). Parts still cartilaginous are represented in stipple.

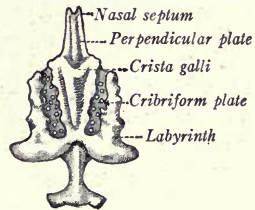


FIG. 319.—Ethmoid bone of a human fetus of four months (modified after Kollmann).

The Ethmoid Bone.—The ethmoid cartilage consists of a mesial mass, which extends from the sphenoid to the tip of the nasal process, and of paired masses lateral to the olfactory fossæ. The lower part of the mesial mass persists as the cartilaginous *nasal septum* but ossification of the upper portion produces the *lamina perpendicularis* and the *crista galli* (Fig. 319). The lateral masses ossify at first into the spongy bone of the ethmoidal labyrinths. From this, the definitive honeycomb structure (*ethmoidal cells*) and the *conchæ* are formed through evaginations of the nasal mucous membrane and the coincident resorption of bone. (Similar invasions of the mucous membrane and dissolution of bone produce the frontal, sphenoidal, and maxillary sinuses; p. 376). Fibers of the olfactory nerve at first course between the unjoined mesial and lateral masses. Later, cartilaginous, and finally, bony trabeculae surround these bundles of nerve fibers, and, as the *cribriiform plates*, interconnect the three masses.

The Temporal Bone.—Several centers of ossification in the periotic capsule unite to form a single center from which the whole cartilage is

transformed into the *petrous* and *mastoid* portions of the temporal bone (Fig. 320). The *mastoid process* is formed after birth by a bulging of the petrous bone, and its internal cavities, the *mastoid cells*, are formed and lined by the evaginated epithelial lining of the middle ear. The *squamosal* and *tympanic* portions of the temporal bone are of intramembranous origin, while the *styloid process* originates from the proximal end of the second, or hyoid branchial arch.

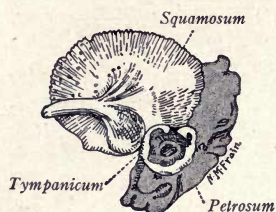


FIG. 320.—The left temporal bone at birth. The portion of intracartilaginous origin is represented in stipple.

Membrane Bones of the Skull.—From the preceding account it is evident that, although the bones forming the base of the skull arise chiefly in cartilage, they receive substantial contributions from membrane bones. The remainder of the sides and roof of the skull is wholly of intramembranous origin, each of the *parietals* forming from a single center, the *frontal* from paired centers. At the incomplete angles between the parietals and their adjacent bones, union is delayed for some time after birth. These membrane-covered spaces constitute the *fontanelles*.

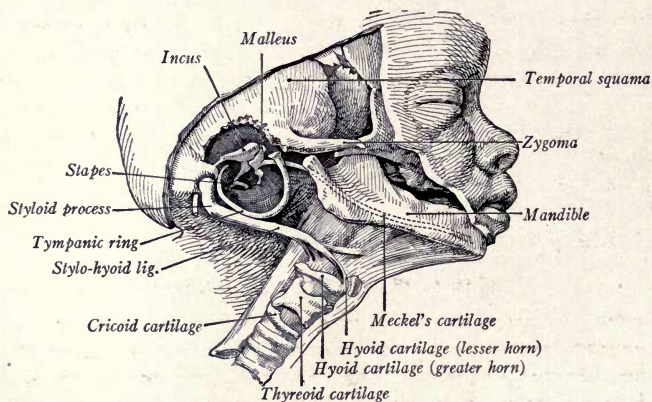


FIG. 321.—Lateral dissection of the head of a human fetus, showing the derivatives of the branchial arches (after Kollmann).

The *vomer* forms from two centers in the connective tissue flanking the lower border of the lamina perpendicularis of the ethmoid. The cartilage of the ethmoid thus invested undergoes resorption.

Single centers of ossification in the mesenchyme of the facial region give rise to the *nasal*, *lacrimal*, and *zygomatic*, all pure membrane bones.

The Branchial Arch Skeleton.—The *first branchial arch* forks into an upper *maxillary* and a lower *mandibular process* (Fig. 119). Cartilage fails to appear in the maxillary processes, due to accelerated development, hence the *palate* bones and the *maxillæ* arise directly in membrane. Each palate bone develops from a single center of ossification. According to one view five centers contribute to the formation of each maxilla; Mall, however, maintains that there are but two centers, one giving rise to the portion bearing the incisor teeth, the other to the remainder of the maxilla.

The entire core of the mandibular process becomes a cartilaginous bar, *Meckel's cartilage*, which extends proximally into the tympanic cavity of the ear (Fig. 321). Membrane bone, developing distally in the future *body*, encloses Meckel's cartilage and the inferior alveolar nerve, whereas proximally in the *ramus* the membrane bone merely lies lateral to these structures—hence the position of the adult *mandibular foramen*. The portion of Meckel's cartilage enclosed in bone disappears, while the cartilage proximal to the mandibular foramen becomes in order, the *spheno-mandibular ligament*, the *malleus*, and the *incus* (p. 389 and Fig. 387).

Each *second branchial arch* comes into relation proximally with the periotic capsule. This upper segment of the cartilage becomes the *stapes* and the *styloid process* of the temporal bone (Figs. 321 and 387). The succeeding distal portion is transformed into the *stylo-hyoid ligament* and connects the styloid process with the distal end of the arch, which also undergoes intracartilaginous ossification to form the *lesser horn* of the hyoid bone.

The cartilage of the *third branchial arches* ossifies and gives origin to the *greater horns* of the hyoid bone, while a plate connecting the two arches becomes its *body*.

The *fourth* and *fifth branchial arches* co-operate in the formation of the *thyreoid cartilage* of the larynx.

THE APPENDICULAR SKELETON

Whereas the axial skeleton originates chiefly from the sclerotomes of the mesodermal segments, the appendicular skeleton is apparently derived from the unsegmented somatic mesenchyme. In embryos of 9 mm., mesenchymal condensations have formed definite blastemal cores in the primitive limb buds (Fig. 323). Following this blastemal stage, the various bones next pass through a cartilaginous stage and finally an osseous one.

The Upper Extremity.—The *clavicle* is the first bone of the skeleton to ossify, centers appearing at each end. Prior to ossification it is composed of a peculiar tissue which makes it difficult to decide whether the bone is intramembranous or intracartilaginous in origin.

The *scapula* arises as a single plate in which there are two chief centers of ossification. One center early forms the *body* and *spine*. The other, after birth, gives rise to the rudimentary *coracoid process*, which in lower vertebrates extends from the scapula to the sternum. Union between the coracoid process and the body does not occur until about the fifteenth year.

The *humerus*, *radius*, and *ulna* ossify from single primary centers and two or more epiphyseal centers (Fig. 296 C-F).

In the cartilaginous *carpus* there is a proximal row of three, and a distal row of four elements. Other inconstant cartilages may appear, and subsequently disappear or become incorporated in other carpal bones. The *pisiform* is regarded as a sesamoid bone which develops in the tendon of the flexor carpi ulnaris; in the same category is the *patella* which forms in the tendon of the quadriceps extensor cruris.

The Lower Extremity.—The cartilaginous plate of the *os coxae* is at first so placed that its long axis is perpendicular to the vertebral column (Fig. 322). Later, it rotates to a position parallel with the vertebral column, and shifts slightly caudal to come into relation with the first three sacral vertebræ. A retention of the membranous condition in the lower half of each primitive cartilaginous plate accounts for the *obturator membrane* which closes the foramen of the same name. Three centers of ossification appear, forming the *ilium*, *ischium*, and *pubis*. The three bones do not fuse completely until about puberty.

The general development of the *femur*, *tibia*, *fibula*, *tarsus*, *metatarsus*, and *phalanges* is quite similar to that of the corresponding bones of the upper extremity.

Anomalies.—Variations in the size, shape, and number of skeletal parts are common. Developmental arrest and over-development are the prime causative factors. Variations in the number of vertebræ (except cervical) are not infrequent. The last cervical and first lumbar vertebræ occasionally bear ribs, due to the continued development of the primitive costal processes. Cleft sternum or cleft xiphoid process represents an incomplete fusion of the sternal bars. Additional fingers or toes (polydactyly) may occur; the cause is obscure. Hare lip and cleft palate have already been mentioned (pp. 148, 151).

II. THE MUSCULAR SYSTEM

The skeletal muscles, with the exception of those attached to the branchial arches, originate from the myotomes of the mesodermal segments (pp. 53, 291 and Fig. 323). Although the primitive segmental arrangement of the myotomes is, for the most part, soon lost, their original innervation by the segmental spinal nerves is retained throughout life. For this reason, the history of adult muscles formed by fusion, splitting, or other modifications may be traced with considerable certainty.

The development of the human musculature is fully described by W. H. Lewis in Keibel and Mall, vol. 1.

Fundamental Processes.—The changes occurring in the myotomes during the formation of adult muscles are referable to the operation of the following fundamental processes:

(1) A *change in direction* of muscle fibers from the original cranio-caudal orientation in the myotome. The fibers of but few muscles retain their initial orientation.

(2) A *migration* of myotomes, wholly or in part, to more or less remote regions. Thus the *latissimus dorsi* originates from cervical myotomes, but finally attaches to the lower thoracic and lumbar vertebræ and to the crest of the ilium. Other examples are the *serratus anterior* and the *trapezius*.

(3) A *fusion* of portions of successive myotomes. The *rectus abdominis* illustrates this process.

(4) A *longitudinal splitting* of myotomes into several portions. Examples are found in the *sterno-* and *omo-hyoid* and in the *trapezius* and *sterno-mastoid*.

(5) A *tangential splitting* into two or more layers. The *oblique* and the *transverse* muscles of the abdomen are formed by the common process.

(6) A *degeneration* of myotomes, wholly or in part. In this way *fascias*, *ligaments*, and *aponeuroses* may be produced.

Muscles of the Trunk.—Ventral extensions grow out from the cervical and thoracic myotomes, and a fusion that is well advanced superficially occurs between all the myotomes in embryos of 10 mm. A dorsal, longitudinal column of fused myotomes, however, can still be distinguished from the sheet formed from the combined ventral prolongations (Fig. 322).

From the superficial portions of the dorsal column there arise by longitudinal and tangential splitting the various *long muscles of the back and neck*, which are innervated by the dorsal rami of the spinal nerves. The deep portions of the myotomes do not fuse, but give rise to the several *intervertebral muscles*, which thus retain their primitive segmental arrangement.

The *muscles of the neck*, other than those innervated by the dorsal rami and those arising from the branchial arches (p. 319) differentiate from ventral extensions of the cervical myotomes. In the same way the *thoraco-abdominal* muscles arise from the more pronounced ventral prolongations of the thoracic myotomes that grow into the body wall along with the ribs (Fig. 322). Reference has already been made to the probable contribution from cervical myotomes to the formation of the diaphragm (p. 189).

The ventral extensions of the lumbar myotomes (except the first) and of the first two sacral myotomes do not participate in the formation

of the body wall. If they persist at all, it is possible that they contribute to the formation of the lower limb. The ventral portions of the third and fourth sacral myotomes give rise to the muscles of the perineal region.

Muscles of the Limbs.—It has generally been believed that the muscles of the extremities are developed from buds of the myotomes which grow

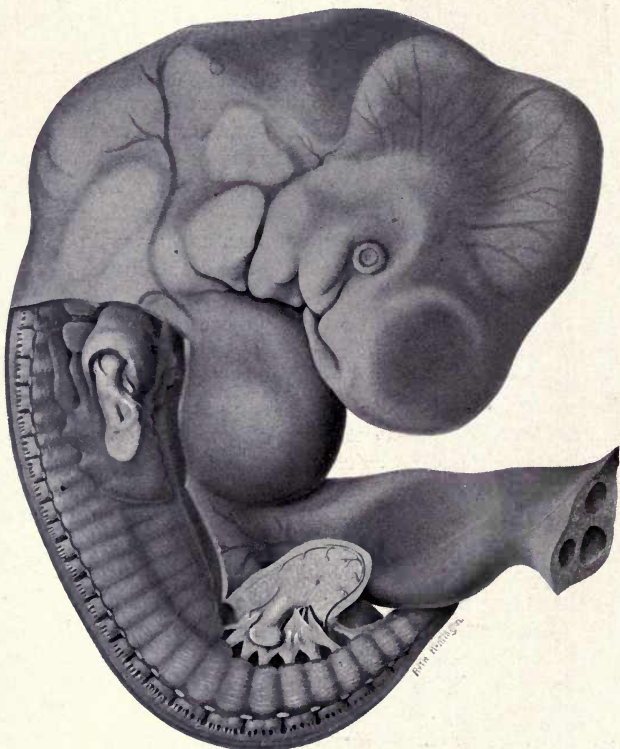


FIG. 322.—Reconstruction of a 9 mm. embryo, to show the partially fused myotomes and the pre-muscle masses of the limbs (Bardeen and Lewis). $\times 13$. Distally, in the upper extremity, the radius, ulna and hand plate are disclosed; in the lower extremity the os coxae and the border vein show.

into the limb anlagen. In sharks this is clearly the case, and in man the segmental nerve supply is suggestive, but not proof, of a myotomic origin. According to Lewis, "there are no observations of distinct myotome buds extending into the limbs" in man. Nevertheless, a diffuse migration of cells from the ventral portion of the myotomes has been recorded by va-

rious observers, recently by Ingalls. These cells soon lose their epithelial character and blend with the undifferentiated mesenchyma of the limb buds (Figs. 322 and 323). From this diffuse tissue, which at about 9 mm. forms premuscle masses, the limb muscles are differentiated, the proximal muscles being the first to appear. The progressive differentiation into distinct muscles reaches the level of the hand and foot in embryos of 20 mm.

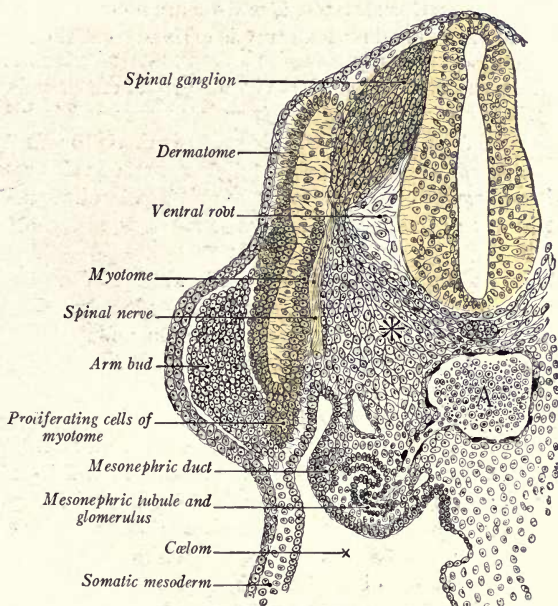


FIG. 323.—Transverse section of a 10.3 monkey embryo, showing the myotome and the mesenchyma of the arm bud (Kollmann). A, aorta; *, sclerotome.

Muscles of the Head.—Distinct mesodermal segments do not occur in the head region. It is possible, however, that a premuscle mass, from which the eye muscles of man are developed, is comparable to three myotomic segments having a similar fate in the shark (cf. p. 366).

The remaining muscles of the head differ from all other skeletal muscles in that they arise from the *splanchnic* mesoderm of the branchial arches and are innervated by nerves (visceral) of a different category than those (somatic) which supply myotomic muscles (p. 356). The mesoderm of the *first branchial arch* gives rise to the muscles of mastication and to all other muscles innervated by the trigeminal nerve. Similarly, the

muscles of expression, and other muscles supplied by the facial nerve, originate from the *second*, or *hyoid arch*. The *third arch* probably gives origin to the pharyngeal muscles, and the *third and fourth arches* to the intrinsic muscles of the larynx.

The *muscles of the tongue* are supplied by the n.hypoglossus, and therefore it has been assumed that they are derived from myotomes of the occipital region (p. 153). According to Lewis, "there is, however, no direct evidence whatever for this statement, and we are inclined to believe from our studies that the tongue musculature is derived from the mesoderm of the floor of the mouth."

Anomalies.—Variations in the form, position, and attachments of the muscles are common. Most of these anomalies are referable to the variable action of the several developmental factors listed on p. 317).

CHAPTER XII

THE MORPHOGENESIS OF THE CENTRAL NERVOUS SYSTEM

In discussing the histogenesis of the nervous tissue the early development of the neural tube has been described as an infolding of the neural plate (Fig. 78) and a closure of the neural groove (Fig. 304). The groove begins to close in embryos of 2 mm. along the mid-dorsal line, near the middle of the body, and the closure extends both cranially and caudally (Fig. 324). Until the end of the third week there still persists an opening

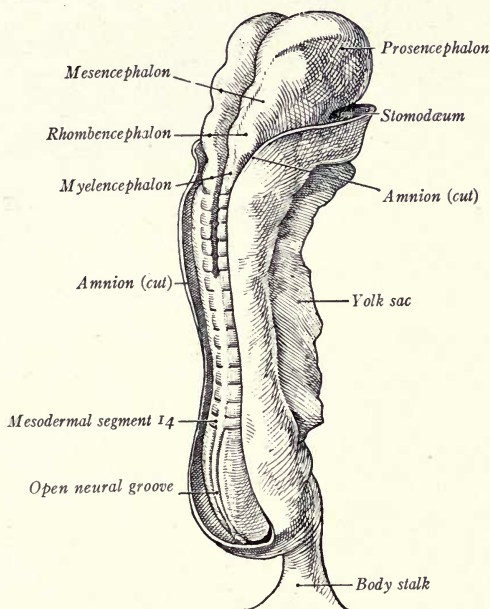


FIG. 324.—Human embryo of 2.4 mm., with a partially closed neural tube (after Kollmann).
× 36.

at either end of the neural tube, somewhat dorsad. These openings are the *neuropores* (Fig. 330). Before the closure of the neuropores, in embryos of 2 to 2.5 mm., the cranial end of the neural tube has enlarged and is constricted at two points to form the three *primary brain vesicles*. The caudal two-thirds of the neural tube, which remains smaller in diameter, constitutes the anlage of the *spinal cord*.

THE SPINAL CORD

The spinal portion of the neural tube is at first nearly straight, but is bent with the flexure of the embryo into a curve which is convex dorsally. Its wall gradually thickens during the first month and the diameter of its cavity is diminished from side to side. By the end of the first month,

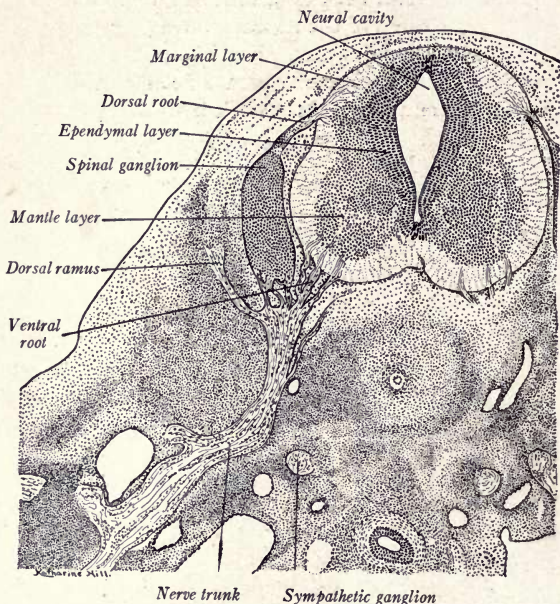


FIG. 325.—Transverse section through a 10 mm. human embryo at the level of the arm buds, showing the spinal cord and a spinal nerve of the right side. $\times 44$.

three layers have been developed in its wall, as described on p. 301 (Fig. 325). These layers are the inner *ependymal layer*, which forms a narrow zone about the neural cavity, the middle *mantle layer*, cellular, and the outer *marginal layer*, fibrous.

The **Ependymal Layer** is differentiated into a *dorsal roof plate* and a *ventral floor plate* (Fig. 326). Laterally, its proliferating cells contribute neuroblasts and neuroglia cells to the mantle layer. The proliferation of cells ceases first in the ventral portion of the layer, which is thus narrower than the dorsal portion in 10 to 20 mm. embryos (Figs. 325 and 326). Consequently, the ventral portion of the mantle layer is differentiated first. The neural cavity is at first somewhat rhomboidal in transverse section,

wider dorsally than ventrally. Its lateral angle forms the *sulcus limitans* (Fig. 334), which marks the subdivision of the lateral walls of the neural

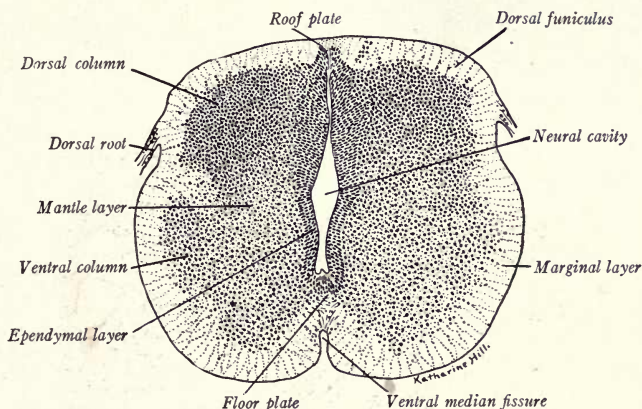


FIG. 326.—Transverse section of the spinal cord from a 20 mm. human embryo. $\times 44$.

tube into the dorsal *alar plate* (sensory) and ventral *basal plate* (motor). When the ependymal layer ceases to contribute new cells to the mantle

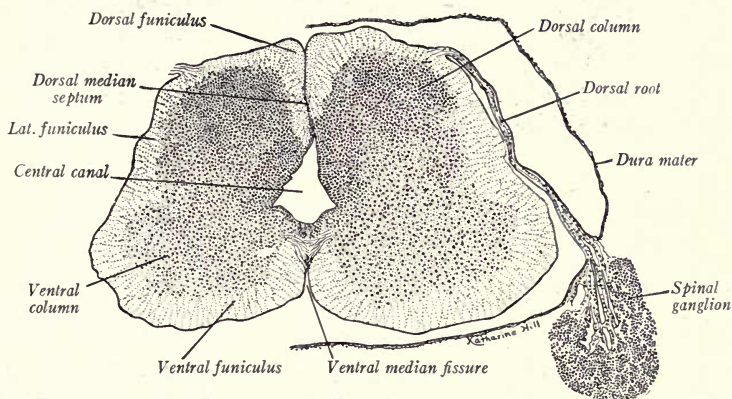


FIG. 327.—Transverse section of the spinal cord from a 34 mm. human embryo, showing also the spinal ganglion and dura mater on the left side. $\times 44$.

layer, its walls are approximated dorsally. As a result, in 20 mm. embryos the neural cavity is wider ventrally (Fig. 326). In the next stage, 34 mm., these walls fuse and the dorsal portion of the neural cavity is obliterated

(Fig. 327). In a 65 mm. (CR) fetus the persisting cavity is becoming rounded (Fig. 328). It forms the *central canal* of the adult spinal cord. The cells lining the central canal are *ependymal cells* proper. Those in the floor of the canal form the persistent *floor plate*. Their fibers extend ventrad, reaching the surface of the cord in the depression of the *ventral median fissure*.

When the right and left walls of the ependymal layer fuse, the ependymal cells of the roof plate no longer radiate, but form a median septum (Fig. 327). Later, as the marginal layers of either side thicken and are

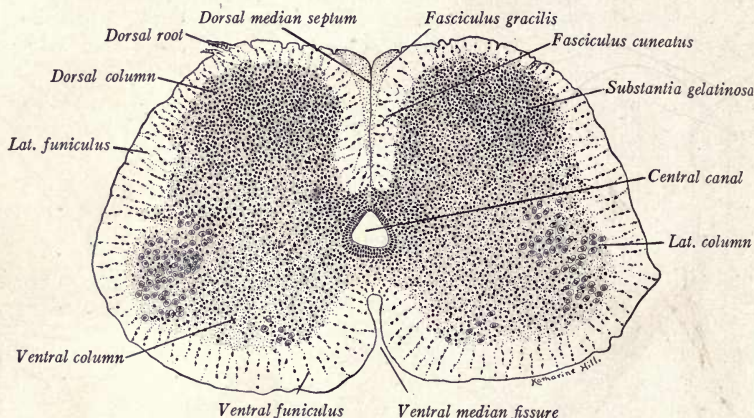


FIG. 328.—Transverse section of the spinal cord from a 65 mm. human fetus. $\times 44$.

approximated, the median septum is extended dorsally. Thus the roof plate is converted into part of the *dorsal median septum* of the adult spinal cord (Fig. 328).

The **Mantle Layer**, as we have seen, receives contributions from the proliferating cells of the ependymal layer. A ventro-lateral thickening first becomes prominent in embryos of 10 to 15 mm. (Fig. 325). This is the *ventral (anterior) gray column*, or *horn*, which in later stages is subdivided, forming also a *lateral gray column* (Fig. 328). It is a derivative of the basal plate. In embryos of 20 mm. a dorso-lateral thickening of the mantle layer is seen, the cells of which constitute the *dorsal (posterior) gray column*, or *horn* (Figs. 327 and 328); about these cells the collaterals of the dorsal root fibers end. The cells of the dorsal gray column, derivatives of the alar plate of the cord, thus form terminal nuclei for the afferent spinal nerve fibers. Dorsal and ventral to the central canal, the mantle layer forms the *dorsal and ventral gray commissures*. In the ventral floor

plate, nerve fibers cross from both sides of the cord and form the *ventral (anterior) white commissure*.

The **Marginal Layer** is composed primarily of a framework of neuroglia and ependymal-cell, processes. Into this framework grow the axons of nerve cells, so that the thickening of this layer is due to the increasing number of nerve fibers contributed to it by extrinsic ganglion cells and neuroblasts. When their myelin develops, these fibers form the white substance of the spinal cord. The fibers have three sources (Fig. 360): (1) they may arise from the spinal ganglion cells, entering as dorsal root fibers and coursing cranially and caudally in the marginal layer; (2) they may arise from neuroblasts in the mantle layer of the spinal cord, (a) as fibers which connect adjacent nuclei of the cord (*fasciculi proprii* or ground bundles), or (b) as fibers which extend upward to the brain; (3) they may arise from neuroblasts of the brain, (a) as descending tracts from the brain stem, or (b) as long, descending cerebrospinal tracts from the cortex of the cerebrum.

Of these fiber tracts, (1) and (2 a) appear during the first month; (2 b) and (3 a) during the third month; (3 b) at the end of the fifth month.

The dorsal root fibers from the spinal ganglion cells, entering the cord dorso-laterally, subdivide the white substance of the marginal layer into a *dorsal funiculus* and *lateral funiculus*. The lateral funiculus is marked off by the ventral root fibers from the *ventral funiculus* (Fig. 327). The ventral root fibers, as we have seen, take their origin from the neuroblasts of the ventral gray column in the mantle layer. They are thus derivatives of the *basal plate*.

The dorsal funiculus is formed chiefly by the dorsal root fibers of the ganglion cells, and is subdivided into two distinct bundles, the *fasciculus gracilis*, median in position, and the *fasciculus cuneatus*, lateral. The dorsal funiculi are separated only by the dorsal median septum (Fig. 328).

The lateral and ventral funiculi are composed: (1) of *fasciculi proprii*, or *ground bundles*, originating in the spinal cord; (2) of ascending tracts from the cord to the brain; (3) of the descending fiber tracts from the brain. The fibers of these fasciculi intermingle and the fasciculi are thus without sharp boundaries. The floor plate of ependymal cells lags behind in its development, and, as it is interposed between the thickening right and left walls of the ventral funiculi, these do not meet and the *ventral median fissure* is produced (cf. Figs. 325 and 328).

The development of myelin in the nerve fibers of the cord begins late in the fourth month of fetal life and is completed between the fifteenth and twentieth years (Flechsig, Bechterew). Myelin appears first in the root fibers of the spinal nerves and in those of the ventral commissure, next in the ground bundles and dorsal funiculi. The cerebrospinal (pyramidal) fasciculi are the last in which myelin is developed; they are myelinated during

the first and second years. As myelin appears in the various fiber tracts at different periods, this condition has been utilized in tracing the extent and origin of the various fasciculi in the central nervous system.

The Cervical and Lumbar Enlargements.—At the levels of the two nerve plexuses supplying the upper and lower extremities, the spinal cord enlarges. As the fibers to the muscles of the extremities arise from nerve cells in the ventral gray column, the number of these cells and the mass of the gray substance is increased; since larger numbers of fibers from the integument of the limbs also enter the cord at this level, there are likewise present more cells about which sensory fibers terminate. There is formed consequently at the level of the origin of the nerves of the brachial plexus the *cervical enlargement*, opposite the origins of the nerves of the lumbo-sacral plexus the *lumbar enlargement* (Fig. 329).

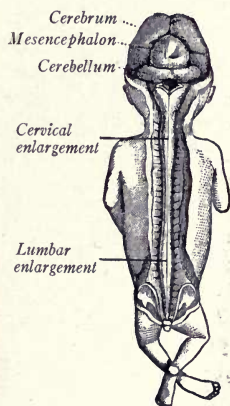


FIG. 329.—Dissection of the brain and cord of a three months' fetus, showing the cervical and lumbar enlargements (after Kölliker in Marshall). Natural size.

At the caudal end of the neural tube of a four months' fetus, an epithelial sac is formed which is adherent to the integument. Cranial to the sac, the central canal is obliterated, this part of the neural tube forming the *filum terminale*. The caudal end of the central canal is irregularly expanded and is known as the *terminal ventricle*.

After the third month the vertebral column grows faster than the spinal cord. As the cord is fixed to the brain, the vertebræ and the associated roots and ganglia of the spinal nerves shift caudally along the cord. The origin of the coccygeal nerves in the adult is opposite the first lumbar vertebra and the nerves course obliquely downward, nearly parallel to the spinal cord. As

the tip of the neural tube is attached to the coccyx, its caudal portion becomes stretched into the slender, solid cord known as the *filum terminale*. The obliquely coursing spinal nerves, with the *filum terminale*, constitute the *cauda equina*.

THE BRAIN

We have seen that in embryos of 2 to 2.5 mm. the neural tube is nearly straight, but that its cranial end is enlarged to form the anlage of the brain (Fig. 324). The appearance of two constrictions in the wall of the anlage subdivides it into the three *primary brain vesicles*—the fore-brain, or *prosencephalon*, mid-brain, or *mesencephalon*, and hind-brain, or *rhombencephalon*.

In embryos of 3.2 mm., estimated age four weeks, three important changes have taken place (Fig. 330): (1) the neural tube is bent sharply in the mid-brain region (the *cephalic flexure*), so that the axis of the fore-brain now forms a right angle with the axis of the hind-brain; (2) the fore-brain shows indication dorsally of a fold, the *margo thalamicus* which subdivides it into the *telencephalon* and the *diencephalon*; (3) the lateral walls of the fore-brain show distinct evaginations, the *optic vesicles*, which project laterad and caudad. A ventral bulging of the wall of the hind-brain indicates the position of the future *pontine flexure*.

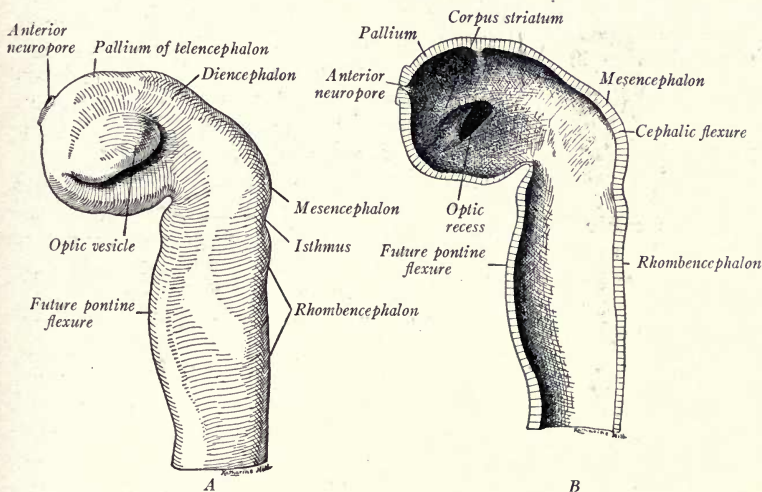


FIG. 330.—Reconstructions of the brain of a 3.2 mm. human embryo (after His). \times about 35.
A, Lateral surface; B, in median sagittal section.

In embryos of 7 mm. (five weeks) the *neuropores* have closed (Fig. 331). The cephalic flexure, now more marked, forms an acute angle, and the pontine flexure, just indicated in the previous stage, is now a prominent ventral band in the ventro-lateral walls of the hind-brain. This flexure forms the boundary line which subdivides the rhombencephalon into a cranial portion, the *metencephalon*, and into a caudal portion, the *myelencephalon*. At a third bend, the whole brain is flexed ventrally at an angle with the axis of the spinal cord. This bend, the *cervical flexure*, is the line of demarcation between the brain and spinal cord (cf. Fig. 333 A). The telencephalon and diencephalon are more distinctly subdivided, and the evaginated optic vesicle forms the *optic cup*, attached to the brain wall by a hollow stalk, in which later grows the

optic nerve. The walls of the brain show a distinct differentiation in certain regions. This is especially marked in the myelencephalon, which has a thicker ventro-lateral wall and thinner dorsal wall.

Embryos of 10.2 mm. show the structure of the brain at the beginning of the second month (Figs. 341 and 344). The five brain regions are now sharply differentiated externally, but the boundary line between the telencephalon and diencephalon is still indistinct. The telencephalon consists of paired, lateral outgrowths, the anlagen of the *cerebral hemispheres* and *rhinencephalon* (olfactory brain). In Fig. 359 the external form of the brain is seen with the origins of the cerebral nerves. It will be noted

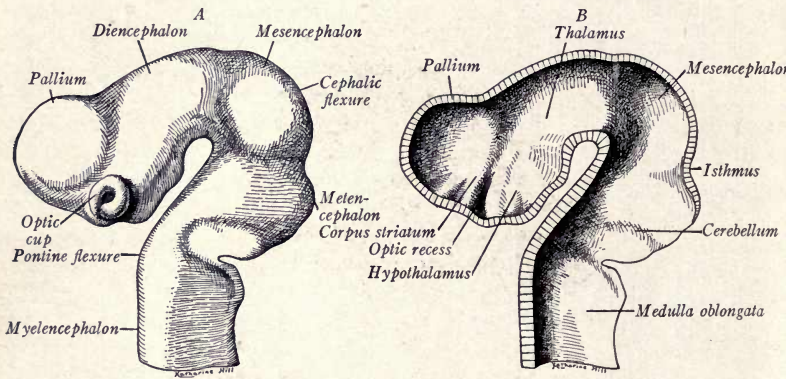


FIG. 331.—Reconstructions of the brain of a 7 mm. human embryo (His). A, Lateral view; B, in median sagittal section.

that, with the exception of the first four (the olfactory, optic, oculomotor, and trochlear), the cerebral nerves take their superficial origin from the myelencephalon.

The cephalic flexure forms a very acute angle, and, as a result, the long axis of the fore-brain is nearly parallel to that of the hind-brain (Fig. 359). The oculomotor nerve takes its origin from the ventral wall of the mesencephalon. Dorsally, there is a constriction, the *isthmus*, between the mesencephalon and metencephalon, and here the fibers of the trochlear nerve take their superficial origin. The dorsal wall of the myelencephalon is an exceedingly thin ependymal layer which becomes the *tela chorioidea*. The ventro-lateral walls of this same region, on the other hand, are very thick.

A median sagittal section of a brain at a somewhat later stage shows the cervical, pontine, and cephalic flexures well marked (Fig. 332; the

thin, dorso-lateral roof of the myelencephalon has been removed). The telencephalon is a paired structure. In the figure, its right half projects cranial to the primitive median wall of the fore-brain, which persists as the *lamina terminalis* (cf. Fig. 342). The floor of the telencephalon is greatly thickened caudally as the anlage of the *corpus striatum*. A slight evagination of the ventral wall of the telencephalon, just cranial to the corpus striatum, marks the anlage of the *rhinencephalon*. The remaining portion of the telencephalon forms the *pallium*, or *cortex*, of the *cerebral hemispheres*. The paired cavities of the telencephalon are the *lateral* (first and second) *ventricles*, and these communicate through the *interven-*

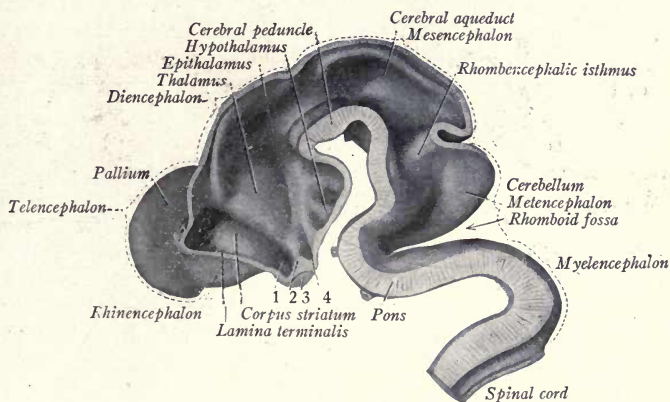


FIG. 332.—Brain of a 13.6 mm. human embryo in median sagittal section (after His in Sobotta).
1, Optic recess; 2, ridge formed by 3, the optic chiasma; 4, infundibular recess.

tricular foramina (of Monro) with the cavity of the diencephalon, the *third ventricle*. The cavities of the olfactory lobes communicate during fetal life with the lateral ventricles and were formerly called the first ventricles.

The crossing of a portion of the optic nerve fibers in the floor of the brain forms the *optic chiasma*, and this, with the transverse ridge produced by it internally, is taken as the ventral boundary line between the telencephalon and diencephalon (Fig. 332). A dorsal depression separates the latter from the mesencephalon. The lateral wall of the diencephalon is thickened to form the *thalamus*, the caudal and lateral portion of which constitutes the *metathalamus*. From the metathalamus are derived the *geniculate bodies*. In the median dorsal wall, near the caudal boundary line of the diencephalon, an outpocketing begins to appear in embryos of

five weeks (Fig. 332). This is the *epithalamus*, which later gives rise to the *pineal body*, or *epiphysis*.

The thalamus is marked off from the more ventral portion of the diencephalic wall, termed the *hypothalamus*, by the obliquely directed *sulcus limitans* (Fig. 341). Cranial to the optic chiasma is the *optic recess*, regarded as belonging to the telencephalon (Fig. 332). Caudal to it, is the pouch-like *infundibulum*, an extension from which, during the fourth week, forms the posterior lobe of the hypophysis. Caudal to the infundibulum, the floor of the diencephalon forms the *tuber cinereum* and the *mammillary recess*; the walls of the latter thicken later and give rise to the *mammillary bodies*. An oblique transverse section through the telencephalon and hypothalamic portion of the diencephalon (Fig. 343) shows the relation of the optic recess to the optic stalk, the infundibulum, and Rathke's pouch, and the extension of the third ventricle, the proper cavity of the diencephalon, into the telencephalon between the corpora striata.

The mesencephalon in 13.6 mm. embryos (Fig. 332) is distinctly marked off from the metencephalon by the constriction which is termed the *isthmus*. Dorso-lateral thickenings form the *corpora quadrigemina*. Ventrally, the mesencephalic wall is thickened to form the *tegmentum* and *crura cerebri*. In the tegmentum are located the nuclei of origin for the *oculomotor* and *trochlear nerves*. The former, as we have seen, takes its superficial origin ventrally, while the trochlear nerve fibers bend dorsad, cross at the isthmus, and emerge on the opposite side. As the walls of the mesencephalon thicken, its cavity later is narrowed to a canal, the *cerebral aqueduct* (of Sylvius).

The walls of the metencephalon are thickened dorsally and laterally to form the anlage of the *cerebellum*. Its thickened ventral wall becomes the *pons* (Varolii). Its cavity constitutes the cranial portion of the *fourth ventricle*.

The caudal border of the pons is taken as the ventral boundary line between the metencephalon and myelencephalon. The myelencephalon forms the *medulla oblongata*. Its dorsal wall is a thin, non-nervous, ependymal layer, which later becomes the *posterior medullary velum*. From its thickened ventro-lateral walls the last eight cerebral nerves take their origin. Its cavity forms the greater part of the fourth ventricle, which opens caudally into the *central canal* of the spinal cord, cranially into the cerebral aqueduct. The increase in the flexures of the brain and the relative growth of its different regions may be seen by comparing the brains of embryos of four, five, and seven weeks (Fig. 333).

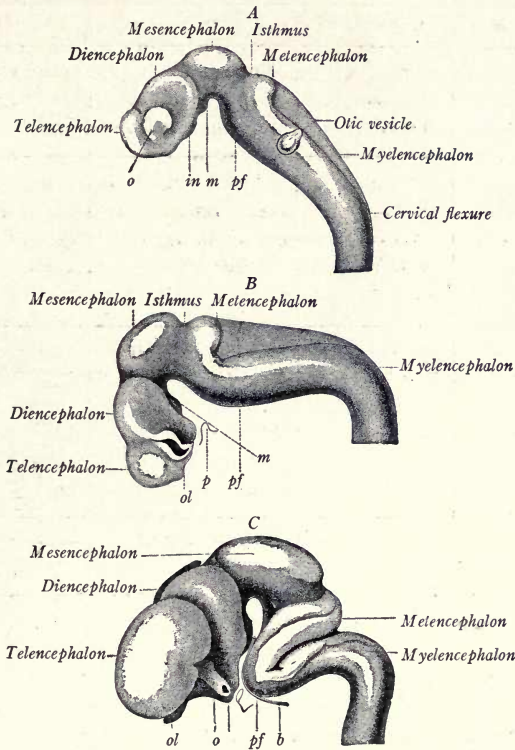


FIG. 333.—Brains of human embryos, from reconstructions by His: *A*, 4.2 mm. embryo (×20); *B*, 6.9 mm. embryo (×16); *C*, 18.5 mm. embryo (×4). *o*, Optic vesicle; *in*, infundibulum; *m*, mammillary body; *pf*, pontine flexure; *ol*, olfactory lobe; *b*, basilar artery; *p*, Rathke's pouch (American Text-Book of Obstetrics).

In the table on page 332 are given the primitive subdivisions of the neural tube and the parts derived from them:

DERIVATIVES OF THE NEURAL TUBE

PRIMARY VESICLES.	SUBDIVISIONS.	DERIVATIVES.	CAVITIES.
Prosencephalon	Telencephalon	Rhinencephalon Cerebral cortex Corpora striata Pars optica hypothalami	Lateral ventricles Cranial portion of third ventricle
	Diencephalon	Epithalamus Thalamus Metathalamus Hypothalamus Hypophysis Tuber cinereum Mammillary bodies	Remainder of third ventricle
Mesencephalon	Mesencephalon	Corpora quadrigemina Tegmentum Crura cerebri	Aqueductus cerebri
Rhombencephalon	Metencephalon	Cerebellum Pons	Fourth ventricle
	Myelencephalon	Medulla oblongata	
Spinal cord		Spinal cord	Central canal.

DIFFERENTIATION OF THE SUBDIVISIONS OF THE BRAIN

The Myelencephalon.—We have seen (p. 322 ff.) that the wall of the spinal cord differentiates dorsally and ventrally into *roof plate* and

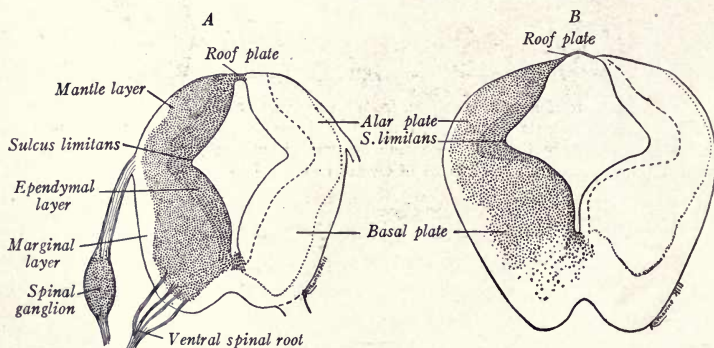


FIG. 334.—Transverse sections from a 10 mm. human embryo. $\times 44$ A, Through the upper cervical region of the spinal cord; B, through the caudal end of the myelencephalon.

floor plate, laterally into the *alar plate* and *basal plate*. The boundary line between the alar and basal plates is the *sulcus limitans* (Fig. 334 A).

The same subdivisions may be recognized in the myelencephalon. It differs from the spinal cord, however, in that the roof plate is broad, thin, and flattened to form the *ependymal layer* (Figs. 334 *B* and 335). In the

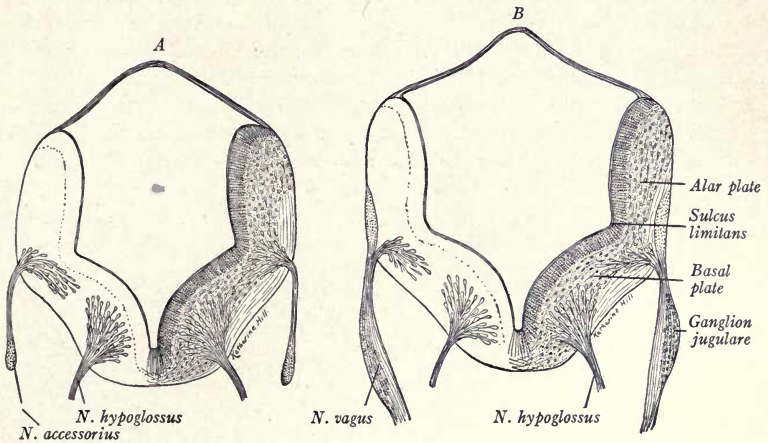


FIG. 335.—Transverse sections through the myelencephalon of a 10.2 mm. embryo (His). $\times 37$. *A*, Through the nuclei of origin of the spinal accessory and hypoglossal nerves; *B*, through the vagus and hypoglossal nerves.

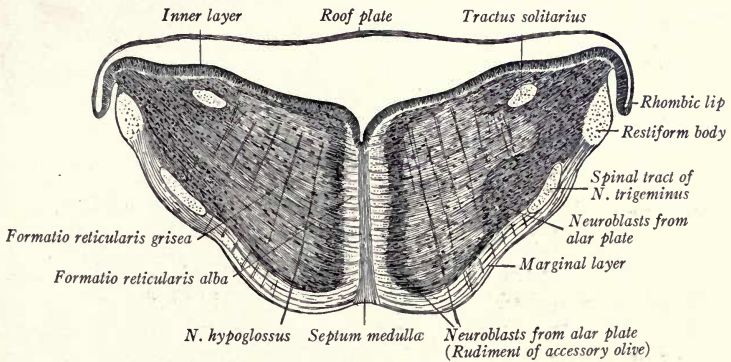


FIG. 336.—Transverse section through the myelencephalon of a 22 mm. embryo (His). $\times 10$.

alar and basal plates of the myelencephalon, the marginal, mantle, and ependymal zones are differentiated as in the spinal cord (Fig. 335). Owing to the formation of the pontine flexure at the beginning of the second month, the roof plate is broadened, especially in the cranial portion of the myelencephalon, and the alar plates bulge laterally (Figs. 336 and

337 A). The cavity of the myelencephalon is thus widened from side to side, and flattened dorso-ventrally. This is most marked cranially, where, between the alar plates of the myelencephalon and metencephalon, are formed the *lateral recesses* of the fourth ventricle (Figs. 337 and 353). Into the ependymal roof of the myelencephalon blood vessels grow, and, invading the lateral recesses, form there the *chorioid plexus* of the fourth ventricle. The plexus consists of small, finger-like folds of the ependymal layer and its covering mesenchymal layer. The line of attachment of the ependymal layer to the alar plate is known as the *rhombic lip* and later becomes the *tania* and *obex* of the fourth ventricle (Fig. 337 B).

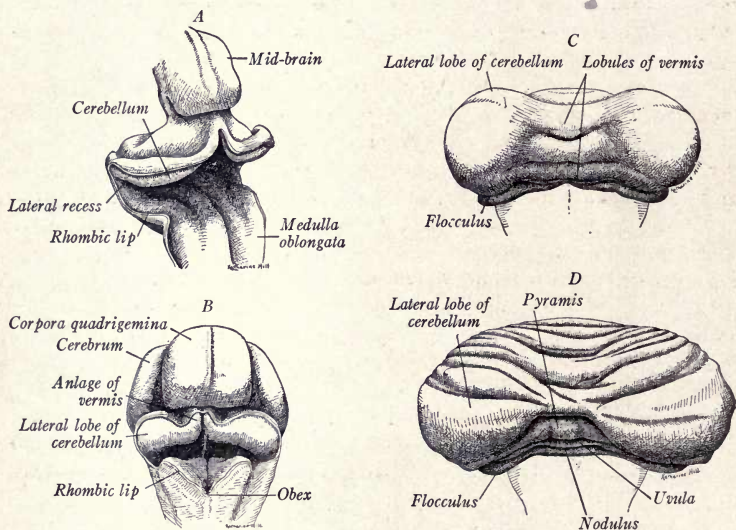


FIG. 337.—Dorsal views of four stages in the development of the cerebellum. A, 13.6 mm. (His); B, 24 mm.; C, 110 mm.; D, 150 mm.

In early stages the floor of the myelencephalon is constricted transversely by the so-called *rhombic grooves*, six in number; the intervals between successive grooves are *neuromeres* (cf. Figs. 96 and 122). Some have viewed these as evidential of a former segmentation of the head similar to that of the trunk. It is more probable, however, that they merely stand in relation to certain cerebral nerves and hence their segmental arrangement is secondary.

The further growth of the myelencephalon is due: (1) to the rapid formation of neuroblasts, derived from the ependymal and mantle layers; (2) to the development of nerve fibers from these neuroblasts; (3) to the

development and growth into it of fibers from neuroblasts in other parts of the brain and spinal cord.

The neuroblasts of the *basal plates* early give rise chiefly to the *efferent fibers* of the cerebral nerves (Fig. 335). They thus constitute motor nuclei of origin of the trigeminal, abducens, facial, glossopharyngeal, vagus complex, and hypoglossal nerves, nuclei corresponding to the ventral and lateral gray columns of the spinal cord. The basal plate likewise produces the *reticular formation*, which is derived in part also from the neuroblasts of the alar plate (Fig. 336). The axons partly cross as *external* and *internal arcuate fibers* and form a portion of the *median longitudinal bundle*, a fasciculus corresponding to the ventral ground bundles of the spinal cord. Other axons grow into the marginal zone of the same side and form *inter-segmental fiber tracts*. The reticular formation is thus differentiated into a *gray portion*, situated in the mantle zone, and into a *white portion* located in the marginal zone (Fig. 336). The marginal zone is further added to by the ascending fiber tracts from the spinal cord and the descending pyramidal tracts from the brain. As in the cord, the marginal layers of each side remain distinct, being separated by the cells of the floor plate.

The *alar plates* differentiate later than the basal plates. The afferent fibers of the cerebral nerves first enter the mantle layer of the alar plates, and, coursing upward and downward, form definite tracts (*tractus solitarius*, *descending tract of fifth nerve*). To these are added tracts from the spinal cord, so that an inner gray and an outer white substance is formed. Soon, however, the cells of the mantle layer proliferate, migrate into the marginal zone, and surround the tracts. These neuroblasts of the alar plate form groups of cells along the terminal tracts of the afferent cerebral nerves (which correspond to the dorsal root fibers of the spinal nerves) and constitute the *receptive*, or *terminal nuclei* of the fifth, seventh, eighth, ninth, and tenth cerebral nerves. Caudally, the *nucleus gracilis* and *nucleus cuneatus* are developed from the alar plates as the terminal nuclei for the afferent fibers which ascend from the dorsal funiculi of the spinal cord. The axons of the neuroblast forming these receptive nuclei decussate through the reticular formation, chiefly as *internal arcuate fibers*, and ascend to the thalamus as the *median lemniscus*.

There are developed from neuroblasts of the alar plate other nuclei, the axons of which connect the brain stem, cerebellum, and fore-brain. Of these the most conspicuous is the *inferior olivary nucleus*.

The characteristic form of the adult myelencephalon is determined by the further growth of the above-mentioned structures. The nuclei of origin of the cerebral nerves, derived from the basal plate, produce swellings in the floor of the fourth ventricle that are bounded laterally by the sulcus limitans. The terminal nuclei of the mixed and sensory cerebral

nerves lie lateral to this sulcus. The enlarged cuneate and gracile nuclei bound the ventricle caudally and laterally as the *cuneus* and *clava*. The inferior olivary nuclei produce lateral, rounded prominences, and ventral to these are the large cerebro-spinal tracts, or *pyramids*.

The Metencephalon.—Cranial to the lateral recesses of the fourth ventricle, the cells of the alar plate proliferate ventrally and form the numerous and relatively large *nuclei of the pons*. The axons from the cells of these nuclei mostly cross to the opposite side and form the *brachium pontis* of the cerebellum. Cerebral fibers from the cerebral peduncles end about the cells of the pontine nuclei. Others pass through the pons as fascicles of the pyramidal tracts.

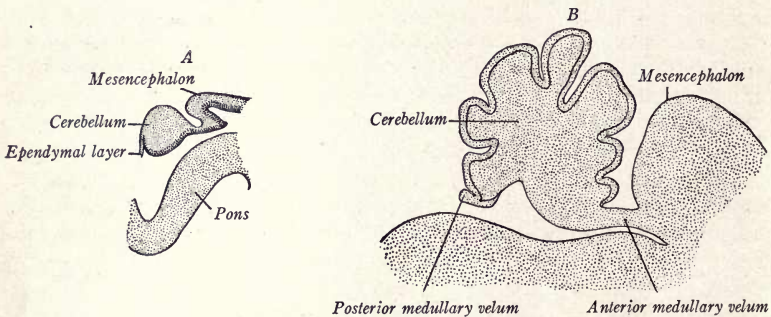


FIG. 338.—Median sagittal sections of the metencephalon and adjoining parts. A, from a 24 mm. embryo; B, from a 150 mm. fetus.

The Cerebellum.—When the alar plates of the cranial end of the myelencephalon are bent out laterally, the caudal portions of their continuations into the metencephalic region are carried laterally also. As a result, the alar plate of the metencephalon takes up a transverse position and forms the anlagen of the *cerebellum* (Fig. 337 A). During the second month the paired cerebellar plates thicken and bulge into the ventricle (Fig. 338 A). Near the mid-line, paired thickenings indicate the anlagen of the *vermis*, while the remainder of the alar plates form the anlagen of the lateral lobes, or *cerebellar hemispheres* (Figs. 337 B and 353).

The cerebellar anlagen grow rapidly both laterally and in length, so that their surfaces are folded transversely. During the third month their walls bulge outward and form on either side a convex *lateral lobe*, connected with the pons by the *brachium pontis* (Fig. 337 C). In the meantime the anlagen of the vermis have fused in the mid-line, producing a single structure marked by transverse fissures. The rhombic lip gives rise to the *flocculus* and *nodulus*. Between the third and fifth months the cortex

cerebelli grows more rapidly than the deeper layers of the cerebellum, and its principal lobes, folds, and fissures are formed (Fig. 337 *C, D*). The hemispheres derived from the lateral lobes are the last to be differentiated. Their fissures do not appear until the fifth month.

Cranial to the cerebellum the wall of the neural tube remains thin dorsally, and constitutes the *anterior medullary velum* of the adult (Fig. 338 *B*). Caudally, the ependymal roof of the fourth ventricle becomes the *posterior medullary velum*. The points of attachment of the vela remain approximately fixed, while the cerebellar cortex grows enormously. As a result, the vela are folded in under the expanding cerebellum (Fig. 338).

The anlagen of the cerebellum show at first differentiation into the same three layers which are typical for the neural tube. During the second and third months, cells from the ependymal, and perhaps from the mantle layer of the rhombic lip migrate to the surface of the cerebellar cortex and give rise to the *molecular* and *granular layers* which are characteristic of the adult cerebellar cortex (Schäfer). The later differentiation of the cortex is only completed at birth, or later. The cells of the granular layer become unipolar by a process of unilateral growth. The Purkinje cells differentiate later. Their axons, and those of entering afferent fibers, form the deep *medullary layer* of the cerebellum.

The cells of the mantle layer may take little part in the development of the cerebellar cortex, but give rise to neuroglia cells and fibers and to the internal nuclei. Of these, the *dentate nucleus* is seen at the end of the third month; later, its cellular layer becomes folded, producing its characteristic convolutions. The fibers arising from its cells form the greater part of the *brachium conjunctivum*.

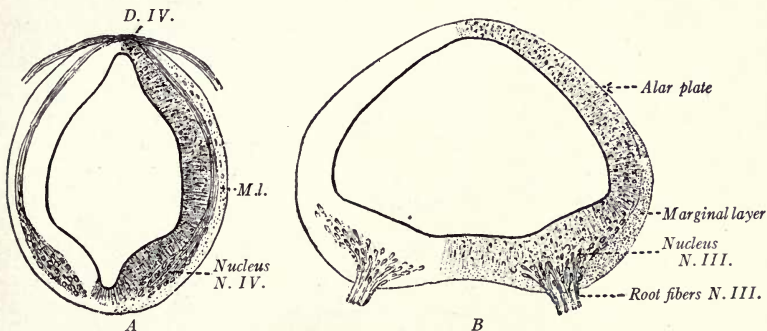


FIG. 339.—Transverse sections through the mesencephalon of a 10.2 mm. embryo (His). *A*, Through the isthmus and origin of the trochlear nerve; *B*, through the nucleus of origin of the oculomotor nerve. *D. IV.*, Decussation of oculomotor nerve; *M.L.*, mantle layer.

The Mesencephalon.—The basal and alar plates can be recognized in this subdivision of the brain, and each differentiates into the three primitive layers (Fig. 339). In the basal plate the neuroblasts give rise to the axons of motor nerves—the oculomotor cranial in position, the trochlear

caudal (Fig. 339 *B*). In addition to these nuclei of origin, the *nucleus ruber* (red nucleus) is developed in the basal plates, ventral and somewhat cranial to the nucleus of the oculomotor nerve. The origin of the cells forming the red nucleus is not definitely known. The alar plates form the paired *superior* and *inferior colliculi*, which together constitute the *corpora quadrigemina* (Figs. 337 *B* and 349). The plates thicken and neuroblasts migrate to their surfaces, forming stratified ganglionic layers comparable to the cortical layers of the cerebellum and the cerebellar nuclei. With the development of the superior and inferior colliculi the cavity of the mesencephalic region decreases in size and becomes the *cerebral aqueduct*.

The mantle layer of the basal plate region is enclosed ventrally and laterally by the fiber tracts which develop in the marginal zone. Ventrally, appear the *median* and *lateral lemnisci*; ventrally, the descending tracts from the cerebral cortex, which together constitute the *peduncles of the cerebrum*, develop later.

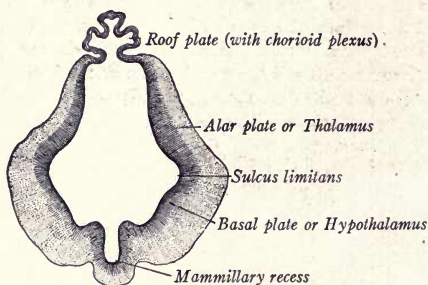


FIG. 340.—Transverse section through the diencephalon of a 13.8 embryo (His). $\times 29$.

The Diencephalon.—In the wall of the diencephalon we may recognize laterally the alar and basal plates, dorsally the roof plate, and ventrally the floor plate (Fig. 340). The roof plate expands, folds as seen in the figure, and into the folds extend blood capillaries. The roof plate thus forms the ependymal lining of the *tela chorioidea* of the third ventricle. The vessels and ingrowing mesenchymal tissue form the chorioid plexus. Cranially, the *tela chorioidea* roofs over the median portion of the telencephalon and is folded laterally into the hemispheres as the *chorioid plexus of the lateral ventricles*. Laterally, the roof plate is attached to the alar plates, and at their point of union are developed the *ganglia habenulae*.

The *epiphysis*, or *pineal body*, is developed caudally as an evagination of the roof plate. It appears at the fifth week (Fig. 335) and is well developed by the third month (Fig. 342). Into the thickened wall of the

anlage is incorporated a certain amount of mesenchymal tissue, and thus the pineal body proper is formed.

The alar plate is greatly thickened and becomes the anlage of the thalamus and metathalamus. The latter, really a part of the thalamus, gives rise to the *lateral* and *median geniculate bodies*.

The *sulcus limitans* (Fig. 341) forms the boundary line between the thalamus (alar plate) and the hypothalamus (basal plate plus the floor plate). The basal plate is comparatively unimportant in the diencephalic

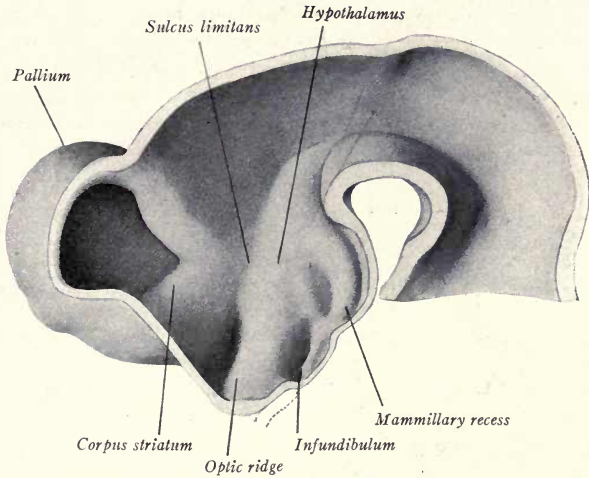


FIG. 341.—Median sagittal section of the fore- and mid-brain from a 10.2 mm. embryo (after His).

region, as no nuclei of origin for motor nerves are developed here. In the floor plate the ridge formed by the optic chiasma constitutes the *pars optica hypothalamica*.

The Hypophysis.—The hypophysis, or pituitary body, has a double origin. Its glandular portions develop from the ectodermal *Rathke's pouch*, which appears at about 3 mm. just in front of the pharyngeal membrane (Fig. 86). This pouch early comes in contact with a sac-like extension of the *infundibulum*, the anlage of the neural hypophyseal lobe (Figs. 122, 341 and 343). Rathke's pouch, at first flat, grows laterally and caudally about the neural lobe, and loses its stalked connection with the oral epithelium at the end of the second month (Fig. 146). The original cavity of the pouch becomes the *residual lumen* of the adult gland. In embryos of about 20 mm., its walls differentiate into the

glandular cords of the *anterior lobe*. That portion of the wall between the lumen and the neural lobe remains thin and constitutes the *pars intermedia*. Recently, a further glandular portion, the *pars tuberalis*,

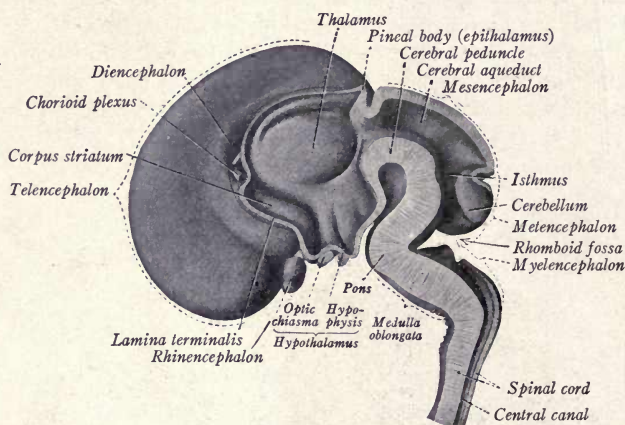


FIG. 342.—Median sagittal section of the brain from a fetus of the third month (His in Sobotta).

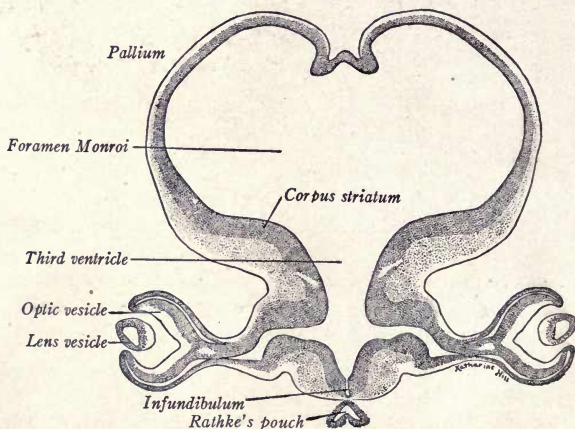


FIG. 343.—Oblique transverse section through the diencephalon and telencephalon of a 10 mm. embryo. $\times 61$.

has been recognized, lying along the tuber cinereum; it develops from the fusion of paired lateral lobes, at the base and in front of Rathke's pouch. The anlage of the neural lobe is transformed into a solid mass of neuroglia

tissue and remains connected to the diencephalon by a permanent infundibular stalk (Fig. 147). The anterior lobe and the pars intermedia elaborate important internal secretions.

Caudal to the infundibulum, in the floor plate, are developed in order the *tuber cinereum* and the *mammillary recess* (Figs. 341, 344 and 346). The lateral walls of the latter thicken and give rise to the paired *mammillary bodies*.

The *third ventricle* lies largely in the diencephalon and is at first relatively broad. Owing to the thickening of its lateral walls, it is compressed until it forms a narrow, vertical cleft. In a majority of adults the thalami are approximated, fuse, and form the *massa intermedia*, or *commissura mollis*, which is encircled by the cavity of the ventricle.

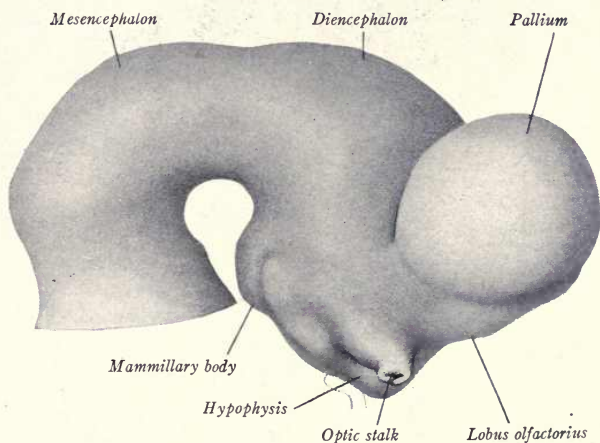


FIG. 344.—Lateral view of the fore- and mid-brains of a 10.2 mm. embryo (His).

The Telencephalon.—This is the most highly differentiated division of the brain (Fig. 344). The primitive structures of the neural tube can no longer be recognized, but the telencephalon is regarded as representing greatly expanded alar plates and is, therefore, essentially a paired structure. Each of the paired outgrowths expands cranially, dorsally, and caudally, and eventually overlies the rest of the brain (Figs. 344, 345 and 346). The telencephalon is differentiated into the *corpus striatum*, *rhinencephalon*, and *pallium* (primitive cortex of cerebral hemisphere). The median lamina between the hemispheres lags behind in its development and thus there is formed the *great longitudinal fissure* between the hemispheres. The lamina is continuous caudally with the roof plate of

the diencephalon; cranially it becomes the *lamina terminalis*, the cranial boundary of the third ventricle (Figs. 332 and 342).

The Chorioid Plexus of the Lateral Ventricles.—It will be remembered (p. 338) that the chorioid plexus of the third ventricle develops in the folds of the roof plate of the diencephalon. Similarly, the thin, median wall of the pallium at its junction with the wall of the diencephalon is folded into the lateral ventricle. A vascular plexus, continuous with that of the third ventricle, grows into this fold, and projects into the lateral

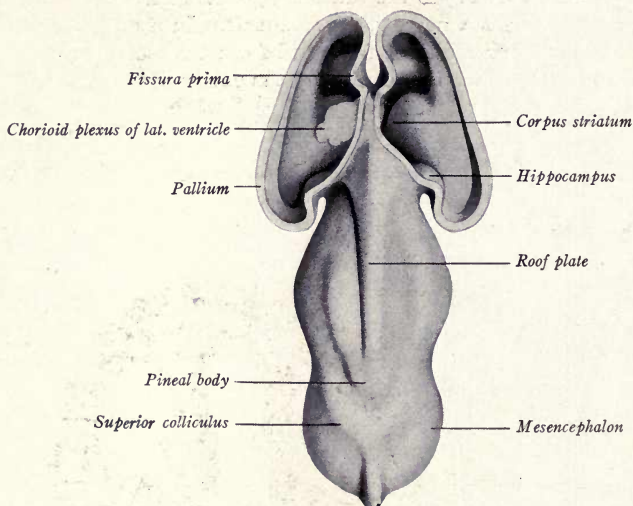


FIG. 345.—The fore-brain and mid-brain of an embryo of 13.6 mm., seen from the dorsal surface. The pallium of the telencephalon is cut away, exposing the lateral ventricle (His).

ventricle of either side (Figs. 345 and 347). The fold of the pallial wall forms the *chorioid fissure* and the vascular plexus is the *chorioid plexus* of the lateral ventricle. This is a paired structure, and, with the plexus of the third ventricle forms a T-shaped figure, the stem of the T overlying the third ventricle, its curved arms projecting into the lateral ventricles just caudal to the interventricular foramen. Later, as the pallium extends, the chorioid plexus of the lateral ventricles and the chorioid fissures are extensively elongated into the temporal lobe and inferior horn of the lateral ventricle (Fig. 348).

The *interventricular foramen* (of Monro) is at first a wide opening (Fig. 343), but is later narrowed to a slit, not by constriction but because its boundaries grow more slowly than the rest of the telencephalon (Fig. 347).

The third ventricle extends some distance into the caudal end of the telencephalon, and laterally in this region the *optic vesicles* develop. Into each optic stalk extends the *optic recess* (Fig. 343).

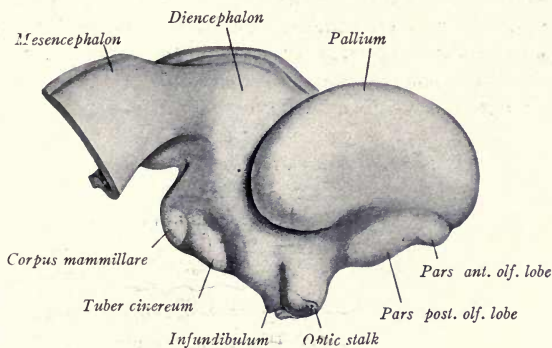


FIG. 346.—Lateral view of the fore-brain and mid-brain of a 13.6 mm. embryo (His).

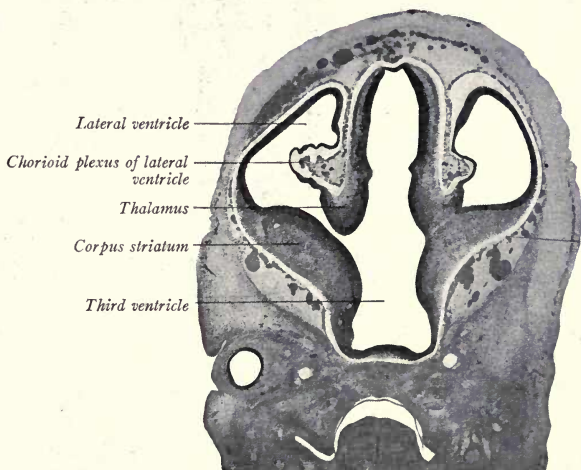


FIG. 347.—Transverse section through the fore-brain of a 15 mm. embryo, showing the early development of the chorioid plexus and fissure (His).

The *corpus striatum* is developed as a thickening in the floor of each cerebral hemisphere (Fig. 331). It is already prominent in embryos of six weeks (13.6 mm.), bulging into the lateral ventricle (Figs. 345 and 347). It is in line caudally with the thalamus of the diencephalon and in develop-

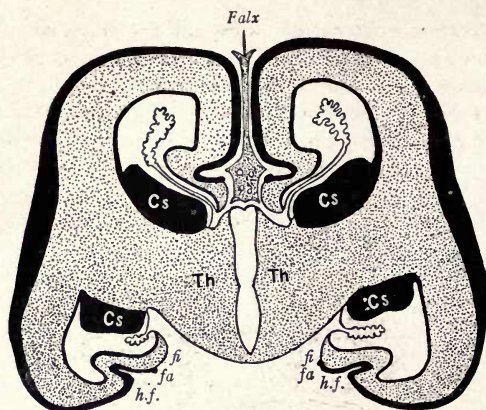


FIG. 348.—A transverse section through the telencephalon of an 83 mm. fetus (after His). *Th*, Thalamus; *Cs*, corpus striatum; *h.f.*, hippocampal fissure; *fa*, marginal gray seam; *fi*, edge of white substance.

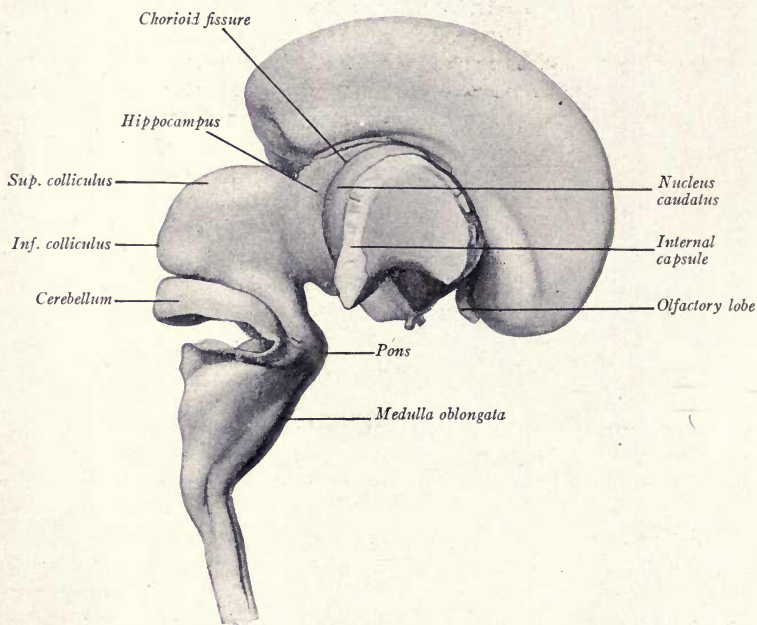


FIG. 349.—Lateral view of the brain of a 53 mm. fetus. The greater part of the pallium of the right cerebral hemisphere has been removed, leaving only that covering the lenticular nucleus, and exposing the internal capsule, caudate nucleus and hippocampus (His).

ment is closely connected with it, although the thalamus always forms a separate structure. The corpus striatum elongates as the cerebral hemisphere lengthens, its caudal portion curving around to the tip of the inferior horn of the lateral ventricle and forming the slender *tail of the caudate nucleus* (Fig. 349). The thickening of the corpus striatum is due to the active proliferation of cells in the ependymal layer which form a prominent mass of mantle layer cells. Nerve fibers to and from the thalamus to the cerebral cortex course through the corpus striatum as laminae which

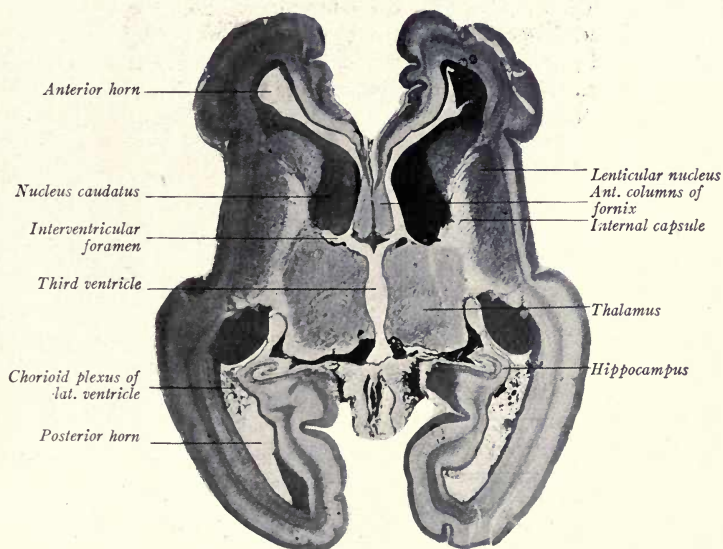


FIG. 350.—Horizontal (coronal) section through the fore-brain of a 160 mm. fetus (His).

are arranged in the form of a wide V, open laterally, when seen in horizontal sections. This V-shaped tract of white fibers is the *internal capsule*, the cranial limb of which partly separates the corpus striatum into the *caudate* and *lenticular nuclei* (Fig. 350). The caudal limb of the capsule extends between the lenticular nucleus and the thalamus.

The thalamus and corpus striatum are separated by a deep groove until the end of the third month (Fig. 347). As the structures enlarge, the groove between them disappears and they form one continuous mass (Fig. 350). According to some investigators there is direct fusion between the two.

The Rhinencephalon.—The olfactory apparatus is divided into a basal portion and a pallial portion. The basal portion consists: (1) of a ventral and cranial evagination (*pars anterior*), formed mesial to the *corpus striatum*, which is the anlage of the *olfactory lobe* and *stalk* (Fig. 346). This receives the olfactory fibers and its cells give rise to *olfactory tracts*. The tubular stalk connecting the olfactory lobe with the cerebrum loses its lumen. (2) Caudal to the anlage of the olfactory lobe a thickening of the brain wall develops (*pars posterior*) which extends mesially along the *lamina terminalis* and laterally becomes continuous with the tip of the temporal lobe (Fig. 346). This thickening constitutes the *anterior perforated space* and the *parolfactory area* of the adult brain (Fig. 356).

The pallial portion of the rhinencephalon is termed the *archipallium* because it forms the entire primitive wall of the cerebrum, a condition which is permanent in fishes and amphibia. Later, when the *neopallium*, or adult cortex, arises, the archipallium forms a median strip of the pallial wall curving along the dorsal edge of the chorioidal fissure from the anterior perforated space around to the tip of the temporal lobe, where it is again connected with the basal portion of the rhinencephalon. The archipallium differentiates into the *hippocampus* (Figs. 345 and 349), a portion of the *gyrus hippocampi*, and into the *gyrus dentatus*. It resembles the rest of the cerebral cortex in the arrangement of its cells. The infolding of the hippocampus produces the *hippocampal fissure*.

Commissures of the Telencephalon.—The important commissures are the *corpus callosum*, *fornix*, and *anterior commissure*. The first is the great transverse commissure of the neopallium, or cerebral cortex, while the fornix and anterior commissure, smaller in size, are connected with the archipallium of the rhinencephalon. The commissures develop in relation to the *lamina terminalis*, crossing partly in its wall and partly in fused adjacent portions of the median pallial walls. Owing to the fusion of the pallial walls dorsal and cranial to it, the *lamina terminalis* thickens rapidly during the fourth and fifth month (Streeter). "It [the *lamina terminalis*] is distended dorsalward and antero-lateralward through the growth of the *corpus callosum*, the shape of which is determined by the expanding pallium." Between the curve of the *corpus callosum* and the fornix, the median pallial walls remain thin and membranous, and constitute the *septum pellucidum* of the adult. The walls of this septum enclose a cavity, the so-called *fifth ventricle*, or *space of the septum pellucidum* (Fig. 351).

The *fornix* takes its origin early, chiefly from cells in the hippocampus. The fibers course along the chorioidal side of the hippocampus cranially, passing dorsal to the foramen of Monro (Fig. 351 A). In the cranial portion of the *lamina terminalis*, fibers are both given off to the basal

portion of the rhinencephalon and received from it. In this region, fibers crossing the midline form the *hippocampal commissure*. Other fibers, as the diverging *anterior pillars* of the fornix, curve ventrally and end in the *mammillary body* of the hypothalamus. The commissure of the hippocampus, originally cranial in position, is carried caudalward with the caudal extension of the corpus callosum (Fig. 351 B).

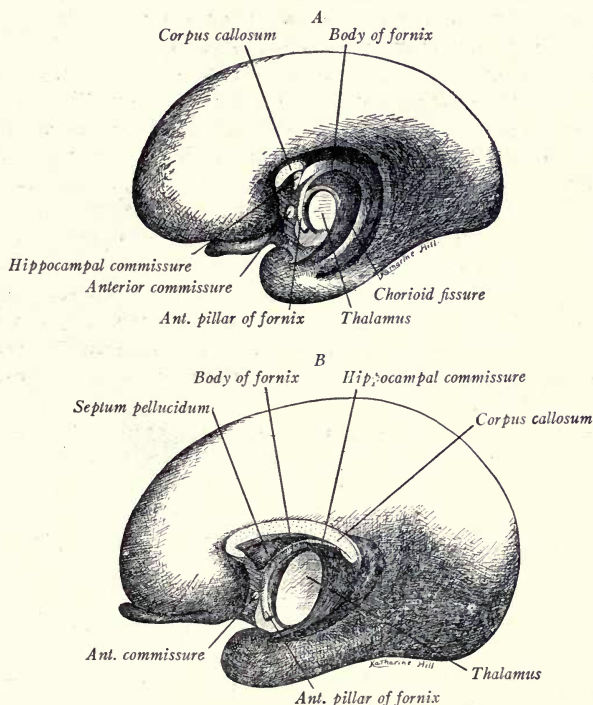


FIG. 351.—Two stages in the development of the cerebral commissure. (Based on reconstructions by His and Streeter). A, Median view of the right hemisphere of an 83 mm. fetus; B, of a 120 mm. fetus.

The fibers of the *anterior commissure* cross in the lamina terminalis ventral to the hippocampal commissure. They arise in a cranial and a caudal division. The fibers of the former take their origin from the olfactory stalk and the adjacent cortex. The fibers of the caudal division pass ventrally about the corpus striatum, between it and the cortex, and may be derived from one or both of these regions.

The *corpus callosum* appears cranial and dorsal to the hippocampal commissure in the roof of the thickened lamina terminalis (Fig. 351 A). Through its fibers, which arise from neuroblasts in the wall of the neopallium (cerebral cortex), nearly all regions of one hemisphere are associated with corresponding regions of the other. With the expansion of the pallium, the corpus callosum is extended cranially and caudally by the development of interstitial fibers. The fibers first found in the corpus

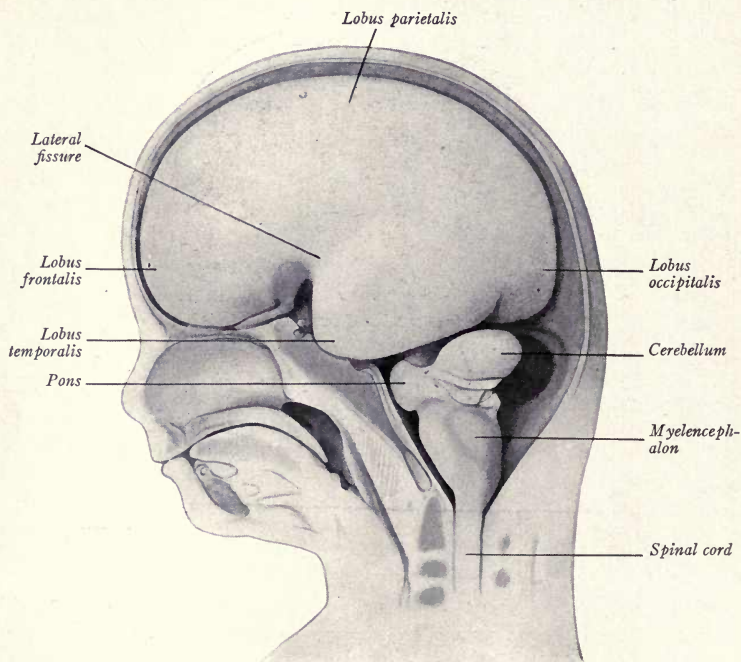


FIG. 352.—Lateral view of the brain of a 90 mm. fetus (His).

callosum arise in the median wall of the hemispheres. In fetuses of five months this great commissure is a conspicuous structure and shows the form which is characteristic of the adult (Fig. 351 B).

Form of the Cerebral Hemispheres.—When the telencephalon expands cranially, caudally, and at the same time ventrally, four lobes may be distinguished (Fig. 352): (1) a cranial *frontal lobe*; (2) a dorsal *parietal lobe*; (3) a caudal *occipital lobe*; and (4) a ventro-lateral *temporal lobe*. The ventricle extends into each of these regions and forms respectively

the *anterior horn*, the *body*, the *posterior horn*, and the *inferior horn* of the lateral ventricle. The surface extent of the cerebral wall, the thin gray cortex, increases more rapidly than the underlying, white medullary layer. As a result, the cortex is folded, producing convolutions between which are depressions, the *fissures* and *sulci*. The *chorioid fissure* is formed, as we have seen (p. 342), by the ingrowth of the chorioid plexus. During the third month the *hippocampal fissure* develops as a curved infolding along the median wall of the temporal lobe. Internally, the infolded

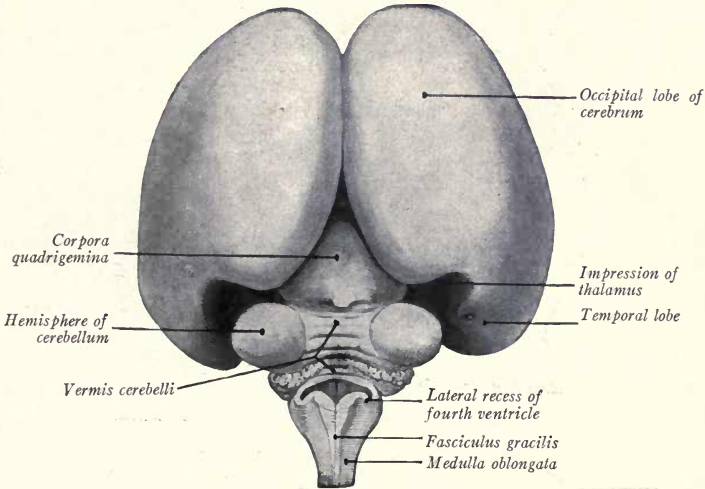


FIG. 353.—Dorsal view of the brain from a 100 mm, fetus (Kollmann).

cortex forms the *hippocampus* (Figs. 345 and 349). The *lateral fissure* (of Sylvius) makes its appearance also in the third month (Fig. 352), but its development is not completed until after birth. The cortex overlying the corpus striatum laterally develops more slowly than the surrounding areas and is thus gradually overgrown by folds of the parietal and frontal lobes (fronto-parietal operculum) and of the temporal lobe (temporal operculum). The area thus overgrown is the *insula* (island of Reil) and the depression so formed is the *lateral fissure* (of Sylvius) (Fig. 355). Later, frontal and orbital opercula are developed ventro-laterally from the frontal lobe. These are not approximated over the insula until after birth. The frontal operculum is included between the anterior limbs of the Sylvian fissure, and the extent of its development, which is variable, determines the form of these limbs.

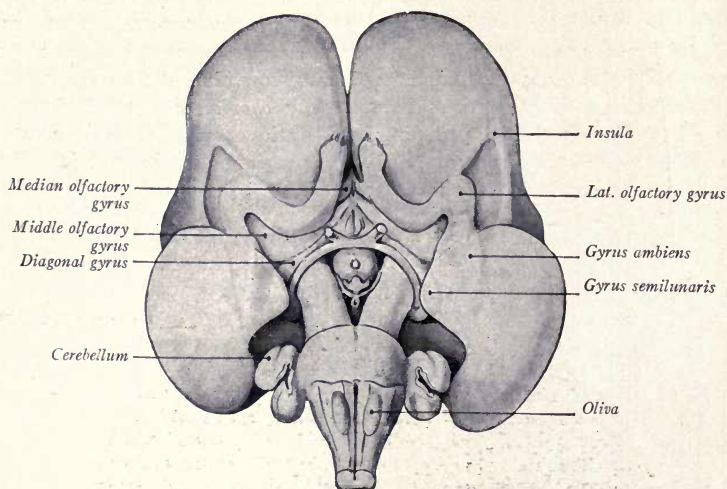


FIG. 354.—Ventral view of the brain of a 100 mm. fetus to show the rhinencephalon (Kollmann)

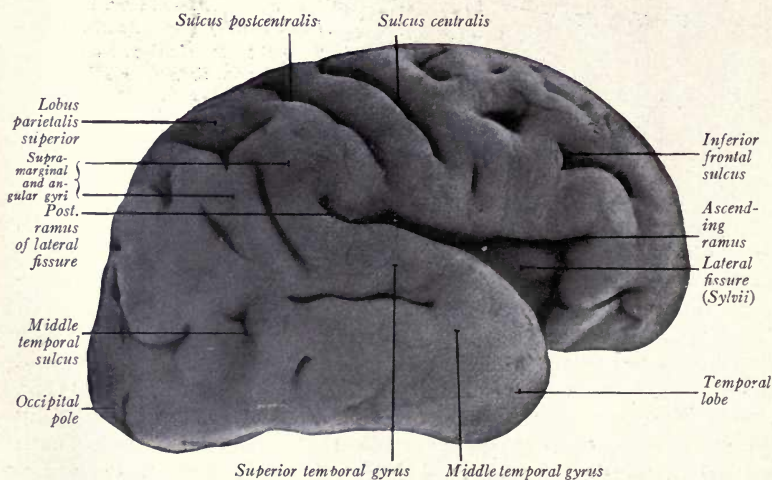


FIG. 355.—Lateral view of the right cerebral hemisphere from a seven months' fetus (Kollmann).

In fetuses of six to seven months, four other depressions appear which later form important landmarks in the cerebral topography. These are: (1) the *central sulcus*, or fissure of Rolando, which forms the dorso-lateral boundary line between the frontal and parietal lobes (Fig. 355); (2) the *parieto-occipital fissure*, which, on the median wall of the cerebrum, is the line of separation between the occipital and parietal lobes (Fig. 356); (3) the *calcarine fissure*, which includes the *cuneus* between itself and the parieto-occipital fissure and marks the position of the visual area of the cerebrum; (4) the *collateral fissure* on the ventral surface of the temporal lobe, which produces the inward bulging on the floor of the posterior horn

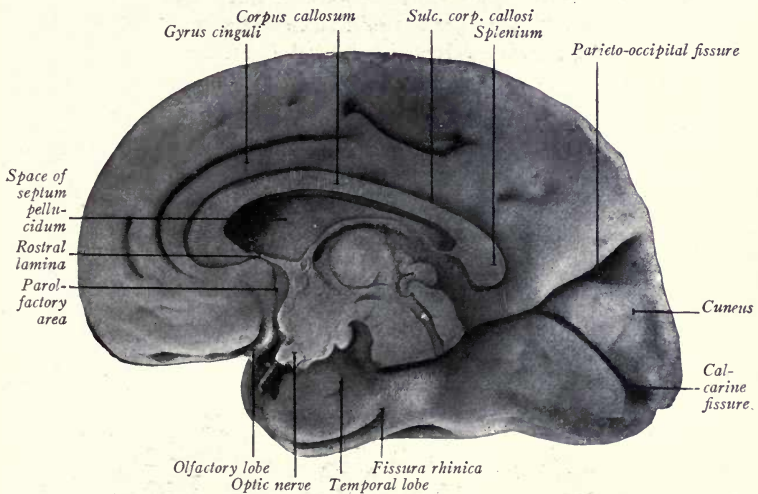


FIG. 356.—Median surface of the right cerebral hemisphere from a seven months' fetus (Kollmann).

of the ventricle known as the *collateral eminence*. The calcarine fissure also affects the internal wall of the ventricle, causing the convexity termed the *calcar avis* (hippocampus minor).

Simultaneously with the development of the collateral fissure, appear other shallower depressions known as *sulci*. These have a definite arrangement, and, with the fissures, mark off from each other the various functional areas of the cerebrum. The surface convolutions between the depressions constitute the *gyri* and *lobules* of the adult cerebrum.

Histogenesis of the Cerebral Cortex.—In the wall of the pallium are differentiated the three primitive zones typical of the neural tube: the endymal, mantle, and marginal layers. During the first two months

the cortex remains thin and differentiation is slow. At eight weeks, neuroblasts migrate from the ependymal and mantle zones into the marginal zone and give rise to layers of pyramidal and other cells typical of the cerebrum. The differentiation of these layers is most active during the third and fourth months, but probably continues until after birth (Mellus, 1912). From the fourth month on, the cerebral wall thickens rapidly, owing to the development: (1) of the fibers from the thalamus and corpus striatum; (2) of endogenous fibers from the neuroblasts of the cortex. The fibers form a white, inner medullary layer surrounded by the gray cortex. Myelination begins shortly before birth (Flechsig), but some fibers may not acquire their sheaths until after the twentieth year. As the cerebral wall increases in thickness the size of the lateral ventricle becomes relatively less, its lateral diameter especially being decreased.

Anomalies.—There are numerous types of defective neural tube development—most the result of arrest. These usually involve the bony investments as well, and produce conspicuous malformations.

The more or less extensive failure of the neural groove to close produces *cranioschisis* (*acrania*), or *rachischisis*, depending on whether the region of the head or vertebral column is affected. If the cleft contains a sac-like protrusion of the membranes, the condition is known as *meningocæle*; if the neural wall alone protrudes, it is *encephalocæle* (brain) or *myelocæle* (spinal cord); if, as is most common, both are involved, it is *meningo-encephalocæle*, or *meningo-myelocæle*. Such a hernial condition of the spine is often called *spina bifida* and is most frequent in the lumbo-sacral region, where the sac may become the size of a child's head.

An excessive fluid content in the brain cavities causes both brain and skull to enlarge, producing *hydrocephaly*.

CHAPTER XIII

THE PERIPHERAL NERVOUS SYSTEM

THE nerves, ganglia, and sense organs constitute the peripheral nervous system. The peripheral nerves consist of bundles of myelinated and unmyelinated *nerve fibers*, and aggregations of nerve cells, the *ganglia*. The fibers are of two types: *afferent fibers*, which carry sensory impulses to the central nervous system, and *efferent fibers*, which carry motor impulses away from the nervous centers. The peripheral *efferent fibers* of both brain and spinal cord take their origin from neuroblasts of the basal plate. Typically they emerge ventro-laterally from the neural tube. Those arising from the spinal cord take origin in the mantle layer, converge, and form the *ventral roots* of the *spinal nerves*. The efferent fibers of the brain take origin from more definite nuclei and constitute the *motor components* of the *cerebral nerves*. The *peripheral afferent fibers* originate from nerve cells which lie outside the neural tube. Those sensory nerve cells related to the spinal cord and to the brain stem caudal to the otic vesicle are derived from the *ganglion crest*, the origin of which has been described (Chapter X, p. 302).

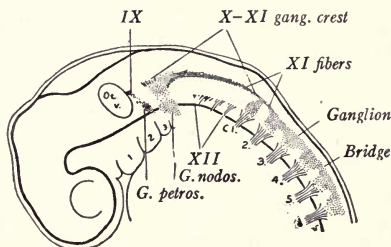


FIG. 357.—Reconstruction of an embryo of 4 mm., showing the development of the cerebro-spinal nerves (Streeter). $\times 17$. C1-6, Cervical spinal nerves.

A. THE SPINAL NERVES

The spinal nerves are segmentally arranged and each consists of dorsal and ventral roots, spinal ganglion, and nerve trunks. In embryos of 4 mm. the ventral roots are already developing as outgrowths of neuroblasts in the mantle layer of the spinal cord (Fig. 357). The spinal ganglia are represented as enlargements along the ganglion crest and are connected by cellular bridges.

In 7 mm. embryos (five weeks old) the cells of the spinal ganglia begin to develop centrally directed processes which enter the marginal zone of

the cord as the *dorsal root fibers* (Fig. 358). These fibers course in the dorsal funiculi and eventually form the greater part of them. Peripheral processes of the ganglion cells join the ventral root fibers in the trunk of the nerve (Fig. 360). At 10 mm. (Fig. 359) the dorsal root fibers have elongated and the cellular bridges of the ganglion crest between the spinal ganglia have begun to disappear. In transverse sections at this

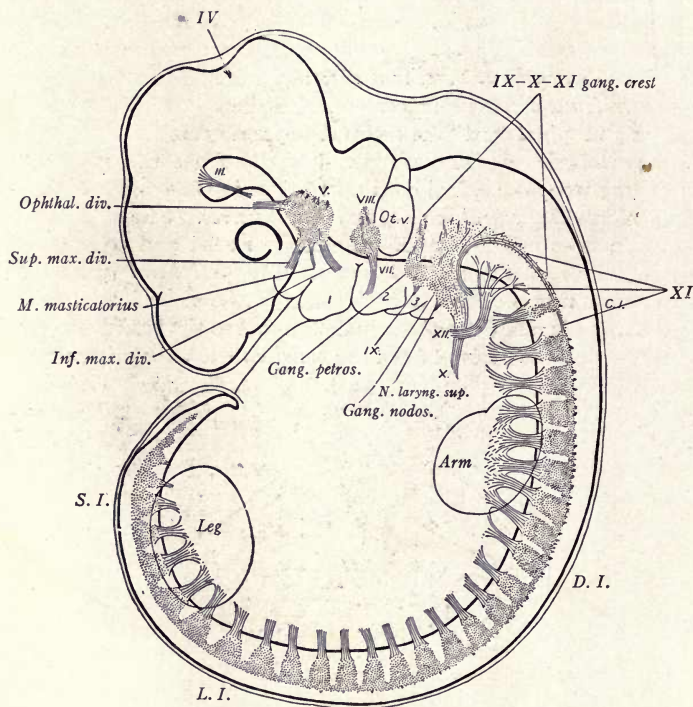


FIG. 358.—Reconstruction of a 6.9 mm. embryo, showing the development of the dorsal root fibers from the spinal and cerebral ganglia* (Streeter). $\times 16.7$.

stage (Fig. 325 and 360) the different parts of a spinal nerve may be seen. The trunk of the nerve, just ventral to the union of the dorsal and ventral roots, gives off laterally the *dorsal*, or *posterior ramus*, the fibers of which supply the dorsal muscles. The *ventral ramus*, continuing, gives off mesially the *ramus communicans* to the sympathetic ganglion, and divides into the *lateral* and *ventral* (anterior) *terminal rami*. The efferent fibers

of these rami supply the muscles of the lateral and ventral body wall, and the afferent fibers end in the integument of the same regions.

At the points where the anterior and lateral terminal rami arise, connecting loops may extend from one spinal nerve to another. Thus, in the cervical region superficial and deep nerve plexuses are formed. The

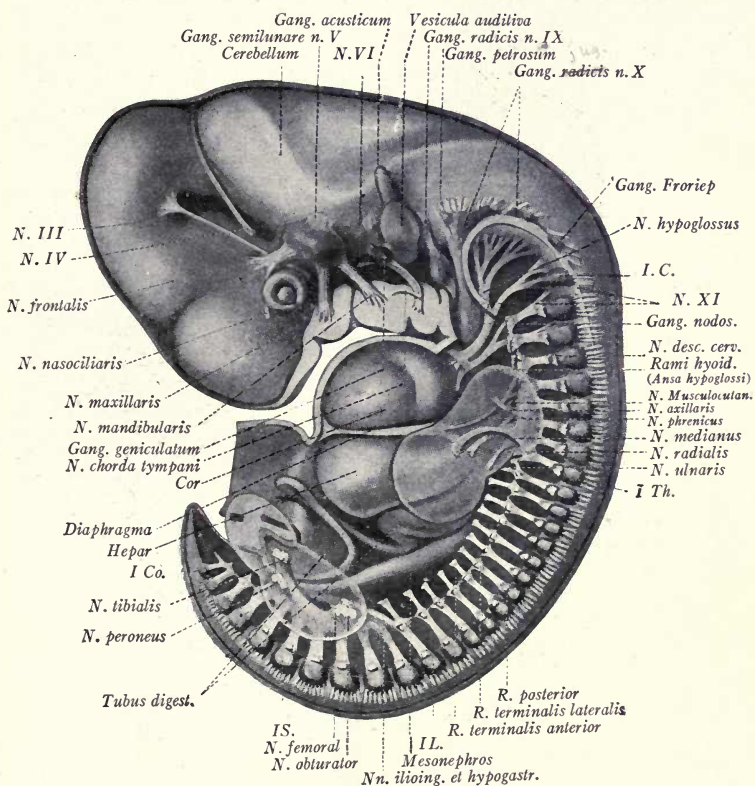


FIG. 359.—Reconstruction of the nervous system of a 10 mm. embryo (Streeter). $\times 12$.

deep cervical plexus forms the *ansa hypoglossi* and the *phrenic nerve* (Fig. 359).

The Brachial and Lumbo-sacral Plexuses.—The nerves supplying the arm and leg also unite to form plexuses. In embryos of 10 mm. (Fig. 359) the trunks of the last four cervical nerves and of the first thoracic are united to form a flattened plate, the anlage of the *brachial plexus*. From this

plate nervous cords extend into the intermuscular spaces and end in the premuscle masses. The developing skeleton of the shoulder splits the brachial plexus into dorsal and ventral laminae. From the dorsal lamina arise the *musculo-cutaneous*, *median*, and *ulna* nerves; from the ventral lamina, the *axillary* and *radial* nerves.

In 10 mm. embryos the lumbar and sacral nerves that supply the leg unite in a plate-like structure, the anlage of the *lumbo-sacral plexus* (Fig. 359). The plate is divided by the skeletal elements of the pelvis and femur into two lateral and two median trunks. Of the cranial pair, the lateral becomes the *femoral* nerve; the median, the *obturator* nerve. The

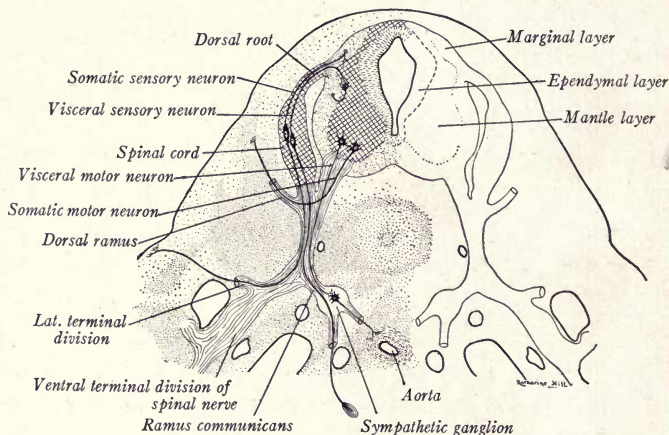


FIG. 360.—Transverse section of a 10 mm. embryo, showing the spinal cord, spinal nerves and their functional nervous components. Diagrammatic.

caudal pair constitutes the *sciatic* nerve; the lateral trunk will be the *peroneal* nerve, the median trunk the *tibial*.

Save for the neurons from the special sense organs (nose, eye, and ear) that form a *special sensory* group, the neurons of the peripheral nerves, both spinal and cerebral, fall into four functional groups (Fig. 360).

(1) *Somatic afferent*, or *general sensory*, with fibers ending in the integument of the body wall.

(2) *Visceral afferent*, or *sensory*, with fibers ending in the walls of the viscera.

(3) *Somatic efferent*, or *motor*, with fibers ending on voluntary muscle fibers.

(4) *Visceral efferent*, or *motor*: (a) with fibers ending about sympathetic ganglion cells, which in turn control the smooth muscle fibers of

the viscera and blood vessels (spinal nerves); or (b) with fibers ending directly on visceral muscle fibers (mixed cerebral nerves).

B. THE CEREBRAL NERVES

The cerebral nerves of the human brain are twelve in number. They differ from the spinal nerves: (1) in that they are not segmentally arranged, and (2) in that they do not all contain the same types of nervous components. Classed according to the functions of their neurons they fall into three groups:

SPECIAL SOMATIC SENSORY.	SOMATIC MOTOR	VISCERAL SENSORY AND MOTOR.
I. Olfactory.	III. Oculomotor.	V. Trigeminal.
II. Optic.	IV. Trochlear.	VII. Facial.
VIII. Acoustic.	VI. Abducens.	IX. Glossopharyngeal.
	XII. Hypoglossal.	X. Vagus complex, including
		XI. Spinal Accessory.

It will be seen: (1) that the nerves of the first group are purely sensory, corresponding to the general somatic afferent neurons of the spinal nerves; (2) that those of the somatic motor group are purely motor and correspond to the somatic efferent neurons of the spinal nerves; (3) that those of the third group are mixed in function and correspond to the visceral components of the spinal nerves.

I. THE SPECIAL SOMATIC SENSORY NERVES

1. The **Olfactory Nerve**, though purely sensory, has no ganglion. Its nerve cells lie at first in the olfactory epithelium of the nose and are of the bipolar type (fourth week). From these cells peripheral processes develop and end directly at the surface of the olfactory epithelium (Fig. 361). Central processes grow toward the olfactory lobe and form the strands of the olfactory nerve. They end in the *glomeruli* of the olfactory bulb in contact with the dendrites of the mitral cells, or olfactory neurons of the second order. Some olfactory cells migrate from the epithelium, with which, however, they retain peripheral connections. Such bipolar cells, found along the entire course of the nerve, resemble ordinary dorsal ganglion cells. The olfactory nerve fibers are peculiar in that they remain unmyelinated. Nerve fibers from the

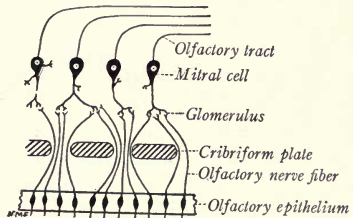


FIG. 361.—Diagram of the relations of the fibers in the olfactory nerve.

epithelium of the vestigial *vomero-nasal organ* (of Jacobson) also end in the olfactory bulb.

When the ethmoidal bone of the cranium is developed, its cartilage, as the cribriform plate, forms around the strands of the olfactory nerve.

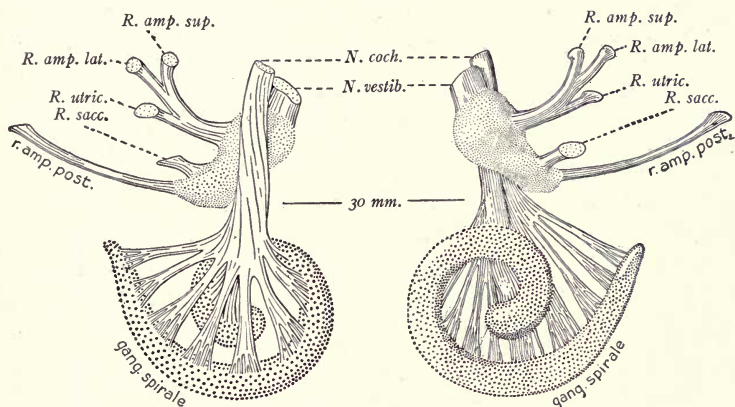
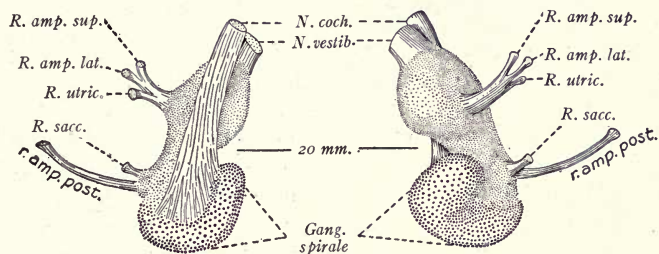
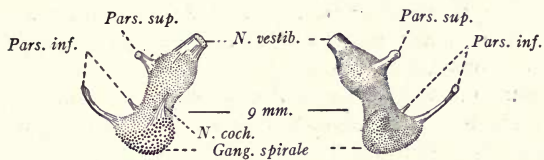
The ganglionated *n. terminalis* courses in close association with the olfactory nerve. Its unmyelinated fibers end in the epithelium of the vomero-nasal organ and of the nose. Although evidently a distinct nerve its significance is obscure.

2. The **Optic Nerve** is formed by fibers which take their origin from neuroblasts in the nervous layer of the retina. The retina is differentiated from an evagination of the wall of the fore-brain (Fig. 343), hence the optic nerve is not a true peripheral nerve, but belongs to the central system of tracts. The neuroblasts from which the optic nerve fibers develop constitute the *ganglion cell layer* of the retina (Fig. 381). During the sixth and seventh weeks these cells give rise to central processes which form a *nerve fiber layer* on the inner side of the retina. The optic fibers converge to the optic stalk and grow through its wall back to the brain. The cells of the optic stalk are converted into a neuroglia framework and the cavity is obliterated. In the floor of the fore-brain, at the boundary between telencephalon and diencephalon, the fibers from the median half of each retina at about the end of the second month cross to the opposite side, and this decussation constitutes the *optic chiasma* (from Greek letter χ , or 'chi'). The crossed and uncrossed fibers constitute the *optic tract* which rounds the cerebral peduncles laterally and dorsally (Fig. 354). Eventually, the optic fibers end in the lateral geniculate body, thalamus, and superior colliculus.

Efferent fibers, terminating in the inner reticular layer of the retina, are also present. In certain fishes where their function has been studied, these fibers resemble visceral efferent components (Arey, 1916).

8. The **Acoustic Nerve** is formed by fibers which grow from the cells of the acoustic ganglion. The origin of these cells is unknown, though they appear in 4 mm. embryos just cranial to the otic vesicle (Fig. 358). The cells become bipolar, central processes uniting the ganglion to the *tuberculum acusticum* of the myelencephalon and peripheral fibers connecting it with the wall of the otocyst.

The acoustic ganglion is differentiated into the *vestibular* and *spiral ganglia* (Fig. 362). The ganglion elongates and is subdivided into superior and inferior portions in 7 mm. embryos. The superior part supplies nerves to the utriculus and to the ampullæ of the anterior and lateral semicircular canals. Part of the inferior portion supplies nerves to the sacculus and to the ampulla of the posterior semicircular canal, and this portion, together with the entire pars superior, constitutes the *vestibular ganglion*.



MEDIAN VIEW

LATERAL VIEW

FIG. 362.—The development of the acoustic ganglia and nerves. The vestibular ganglion is finely stippled, the spiral ganglion coarsely stippled (Streeter).

The greater part of the pars inferior is, however, differentiated into the *spiral ganglion*, the peripheral fibers of which innervate the hair cells of the spiral organ (of Corti) in the cochlea. The spiral ganglion appears in 9 mm. embryos and conforms to the spiral turns of the cochlea, hence its name. Its central nerve fibers form the cochlear division of the acoustic nerve. This is distinctly separated from the central fibers of the vestibular ganglion which constitute the vestibular division of the acoustic nerve, the fibers of which are equilibratory in function. The pars inferior of the vestibular ganglion becomes closely connected with the n. cochlearis, and thus in the adult it appears as though the sacculus and posterior ampulla were supplied by the cochlear nerve.

II. THE SOMATIC MOTOR NERVE

The nerves of this group, consisting of the three nerves to the eye muscles and the n. hypoglossus, are purely motor nerves, the fibers of which take origin from the neuroblasts of the basal plate of the brain stem, near the midline. They are regarded as the homologues of the ventral motor roots of the spinal cord, but they have lost their segmental arrangement and are otherwise modified. The nuclei of origin of these nerves are shown in Fig. 364.

12. The **Hypoglossal Nerve** is formed by the fusion of the ventral root fibers of three to five precervical nerves. Its fibers take origin from neuroblasts of the basal plate and emerge from the ventral wall of the myelencephalon in several groups (Figs. 357 and 364). In embryos of five weeks (7 mm.) the fibers have converged ventrally to form the trunk of the nerve (Fig. 358). Later they grow cranially, lateral to the ganglion nodosum, and eventually end in the muscle fibers of the tongue (Fig. 359). The nerve in its development unites with the first three cervical nerves to form the *ansa hypoglossi*.

That the hypoglossal is a composite nerve, homologous with the ventral roots of the spinal nerves, is shown: (1) by the segmental origin of its fibers; (2) from the fact that its nucleus of origin is a cranial continuation of the ventral gray column, or nucleus of origin for the ventral spinal roots; (3) from the fact that in mammalian embryos (pig, sheep, cat, etc.) rudimentary dorsal ganglia are developed, one of which at least (Froriep's ganglion) sends a dorsal root to the hypoglossal. In human embryos Froriep's ganglion may be present as a rudimentary structure (Figs. 359 and 363), or it may be absent and the ganglion of the first cervical nerve may also degenerate and disappear. In pig embryos Prentiss (1910) has found one to four accessory ganglia (including Froriep's) from which dorsal roots extend to the root fascicles of the hypoglossal nerve (Fig. 121).

3. The **Oculomotor Nerve** originates from neuroblasts in the basal plate of the mesencephalon (Fig. 339 *B*). The fibers emerge as small fascicles on the ventral surface of the mid-brain in the concavity due to the

cephalic flexure (Figs. 359 and 364). The fascicles converge, form the trunk of the nerve, and end in the premuscle masses of the eye. The nerve eventually supplies all of the extrinsic muscles of the eye save the superior oblique and external rectus. A branch also passes to the *ciliary ganglion*. In the chick embryo, bipolar cells migrate along the fibers of the oculomotor nerve to take part in the development of the ganglion. The ciliary ganglion of human embryos is derived entirely from the semilunar ganglion of the trigeminal nerve.

4. The **Trochlear Nerve** fibers take their origin from neuroblasts of the basal plate, located just caudal to the nucleus of origin of the oculomotor nerve (Fig. 364). They are directed dorsally, curve around the cerebral aqueduct, and, crossing in its roof, emerge at the isthmus (Fig. 339 A). From their superficial origin, each is directed ventrally as a slender nerve which connects with the anlage of the superior oblique muscle of the eye (Fig. 359).

6. The **N. Abducens** takes origin from a nucleus of cells in the basal plate of the myelencephalon, located directly beneath the fourth neuromere of the floor of the fourth ventricle (Figs. 359 and 364). The converging fibers emerge ventrally at a point caudal to the future pons, and, as a single trunk, course cranially, mesial to the semilunar ganglion, finally ending in the anlage of the external rectus muscle of the eye. Vestigial rootlets of the abducens and hypoglossal nerve tend to fill in the gap between these two nerves, according to Bremer and Elze.

III. THE VISCERAL MIXED NERVES

The nerves of this group, the trigeminal, facial, glossopharyngeal, and vagus complex (vagus plus the spinal accessory), are mixed in function. The trigeminal nerve, beside its visceral nerve components, contains also numerous somatic sensory neurons which supply the integument of the head and face.

The facial, glossopharyngeal, and vagus nerves are essentially visceral in function. Their sensory fibers, chiefly of the visceral type, supply the sense organs of the branchial arches and viscera. A few somatic sensory fibers, having the same origin and course in the myelencephalon, supply the adjacent integument.

5. The **Trigeminal Nerve** is largely sensory. Its *semilunar ganglion*, a derivative of the ganglion crest, is the largest of the whole nervous system, but very early is distinct from the other cerebral ganglia (Fig. 358). It arises laterally at the extreme cranial end of the hind-brain. Central processes from its cells form the large sensory root of the nerve that enters the wall of the hind-brain at the level of the pontine flexure (Fig. 359). These fibers fork and course cranially and caudally in the alar plate of the

myelencephalon. The caudal fibers constitute the *descending spinal tract* of the trigeminal nerve, which extends as far caudal as the spinal cord (Fig. 364). The peripheral processes separate into three large divisions, the *ophthalmic*, *maxillary*, and *mandibular rami*, and supply the integument of the head and face, and the epithelium of the mouth and tongue.

The motor fibers of the trigeminal nerve arise chiefly from a dorsal motor nucleus that lies opposite the point at which the sensory fibers enter the brain wall (Fig. 364). In the embryo these fibers emerge as a sepa-

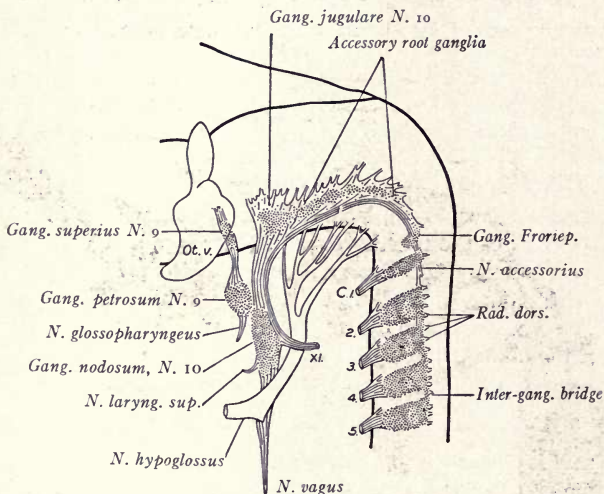


FIG. 363.—Reconstruction of the cerebral nerves of an embryo of 10.2 mm. (Streeter). $\times 16.7$.

rate motor root, course along the mesial side of the semilunar ganglion, and, as a distinct trunk, supply the premuscle masses which later form the muscles of mastication. From the chief motor nucleus, a line of cells extending cranially into the mesencephalon constitutes a second source of origin for motor fibers. In the adult, the motor fibers form a part of the mandibular division of the nerve.

7. The **Facial Nerve** is largely composed of efferent motor fibers that supply the facial muscles of expression. In 10 mm. embryos these fibers arise from a cluster of neuroblasts in the basal plate of the myelencephalon, located beneath the third rhombic groove or neuromere (Fig. 364). The fibers from these cells course laterally, and emerge just mesial to the acoustic ganglion. The motor trunk then courses caudally and is lost in the tissue of the hyoid visceral arch, tissue which later gives rise to the muscles of expression (Fig. 359). The sensory fibers of the facial nerve arise from the

fibers course laterally beneath the spinal tract of the trigeminal nerve and emerge to form the trunk of the nerve. These fibers later supply the muscles of the pharynx.

The sensory fibers of the glossopharyngeal nerve arise from two ganglia, a *superior*, or root ganglion, and a *petrosal*, or trunk ganglion (Figs. 359 and 365). These fibers constitute the greater part of the nerve and divide peripherally to form the *tympenic* and *lingual rami* to the second and third branchial arches. Centrally, these fibers enter the alar plate of the myelencephalon and join the sensory fibers of the facial nerve coursing caudally in the *solitary tract*.

10, 11. The Vagus and Spinal Accessory.—The vagus, like the hypoglossal, is composite. It represents the union of several nerves which supply the branchial arches of aquatic vertebrates (Figs. 359 and 365). The more caudal fascicles of motor fibers take their origin in the lateral gray column of the cervical cord as far back as the fourth cervical segment. These fibers emerge laterally, and, as the *spinal accessory trunk* (in anatomy a distinct nerve), course cephalad along the line of the neural crest (Figs. 358, 359 and 365). Other motor fibers take their origin from the neuroblasts of the *nucleus ambiguus* of the myelencephalon (Fig. 364). Still others arise from a dorsal motor nucleus that lies median in position. The fibers from these two sources emerge laterally as separate fascicles and join the fibers of the spinal accessory in the trunk of the vagus nerve. The *accessory fibers* soon leave the trunk of the vagus and are distributed laterally and caudally to the visceral pre-muscle masses which later form the *sterno-cleido-mastoid* and *trapezius* muscles of the shoulder (Fig. 359). Other motor fibers of the vagus supply muscle fibers of the pharynx and larynx.

As the vagus is a composite nerve, it has several root ganglia which arise as enlargements along the course of the ganglion crest (Figs. 359 and 365). The more cranial of these ganglia is the *ganglion jugulare*. The others, termed *accessory ganglia*, are vestigial structures and not segmentally arranged. In addition to the root ganglia of the vagus, the *ganglion nodosum* forms a ganglion of the trunk (Fig. 365). The trunk ganglia of both the vagus and glossopharyngeal nerves are believed to be derivatives of the ganglion crest, their cells migrating ventrally in early stages.

The central processes from the neuroblasts of the vagus ganglia enter the wall of the myelencephalon, turn caudalward, and, with the sensory fibers of the facial and glossopharyngeal nerves, complete the formation of the *solitary tract*. The peripheral processes of the ganglion cells form the greater part of the vagus trunks after the separation from it of the spinal accessory fibers.

In aquatic vertebrates, special somatic sensory fibers from the *lateral line organs* join the facial, glossopharyngeal, and vagus nerves, and their ganglion cells form part of the geniculate, petrosal, and nodose ganglia. In human embryos the organs of the lateral line are represented by ectodermal thickenings, or *placodes*, which occur tempo-

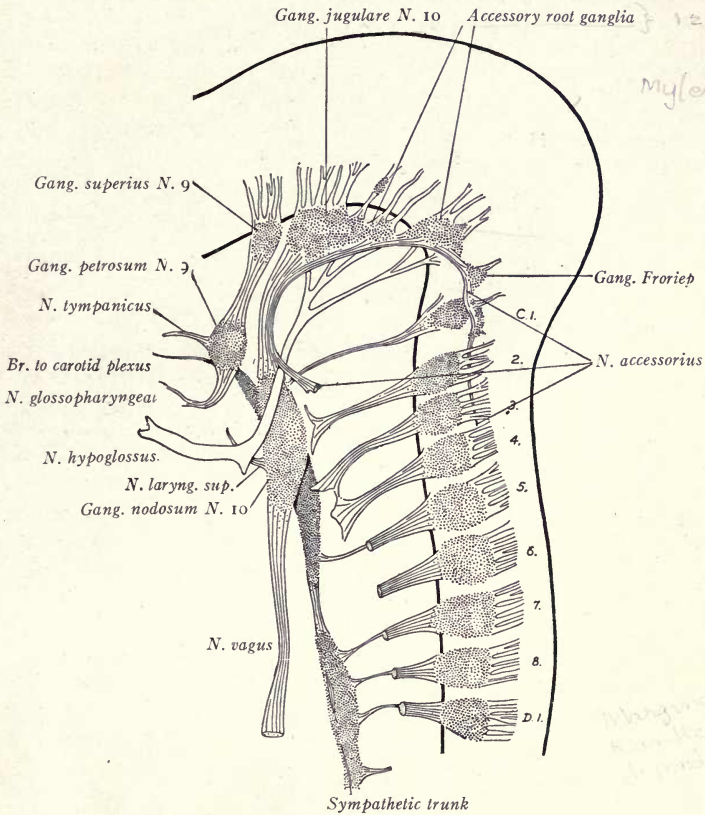


FIG. 365.—A reconstruction of the peripheral nerves in an embryo of 17.5 mm. (Streeter).
× 16.7.

rarily over these ganglia. The nervous elements supplying these vestigial organs have completely disappeared.

Segmentation of the Vertebrate Head.—The vertebrate head undoubtedly consists of fused segments. This was suggested to the earlier workers by the arrangement of the branchial arches (*branchiomerism*), and by the discovery, in the embryos of lower vertebrates, of so-called *head cavities*, homologous with mesodermal segments. (Note also the presence of neuromeres, p. 334.)

Assuming that the branchiomeres are portions of the primary head segments—and there are recent observations which tend to disprove this—their segmentation is still not comparable to that of the trunk, for the branchial arches are formed by the segmentation of *splanchnic* mesoderm, tissue which in the trunk never segments. The branchial arches, therefore, represent a different sort of metamerism.

Only the first three head cavities persist. These form the eye muscles, innervated by the third, fourth, and sixth cerebral nerves respectively. All the remaining muscles of the head are derived from the branchiomeres. From what has been said, it is evident that one cannot compare the relation of the cranial nerves to the branchiomic muscles with the relation of a spinal nerve to its myotomic muscles. For this reason, the cerebral nerves furnish unreliable evidence as to the primitive number of cephalic segments. Various investigators have set this number between eight and nineteen.

C. THE SYMPATHETIC NERVOUS SYSTEM

The sympathetic nervous system is composed of a series of ganglia and peripheral nerves, the fibers of which supply gland cells and the smooth muscle fibers of the viscera and blood vessels. It is also known as the *autonomic system*, for it has a certain degree of independence of the central nervous system.

The sympathetic ganglion cells are derived from the cells of the ganglion crest. In fishes, discrete cellular masses become detached from the spinal ganglia. At an early stage (6 to 7 mm.) in human development, on the contrary, certain cells of the ganglion crest (and neural tube; Kuntz, 1910) migrate ventrally along the nerve roots and give rise to a series of ganglia, which, in the region of the trunk, are segmentally arranged (Fig. 360).

The cells which are to form the ganglia of the sympathetic chain migrate ventrally in advance of the ventral root fibers and take up a position lateral to the aorta (Fig. 325). These sympathetic anlagen are at first distinct, but at 9 mm. unite with each other from segment to segment, forming a longitudinal ganglionated cord. After the formation of the primitive rami communicaates by root fibers from the spinal nerves, centripetal processes from the sympathetic cells grow back and join the trunks of the spinal nerves. The visceral, spinal fibers later become myelinated and constitute the *white rami*; the sympathetic, centripetal fibers remain unmyelinated and form separately the *gray rami*. Nerve fibers appear in the paired longitudinal cords, which were at first purely cellular, in such a manner that segmental masses of cells (*sympathetic ganglia*) become linked by fibrous, commissural cords. The more peripheral ganglia (cardiac and coeliac) and the sympathetic ganglia of the head may be found in 16 mm. embryos (Fig. 366).

In the head region the sympathetic ganglia are not segmentally arranged, but are derived from cells of the cerebrospinal ganglia that migrate to a ventral position (Fig. 365). These cells likewise give rise to nerve

fibers which constitute longitudinal commissures and connect the various ganglia of the head with the ganglionated cord of the trunk region. The small, cranial sympathetic ganglia are probably all derived from the anlage of the semilunar ganglion (Fig. 366). The *ciliary ganglion* is related by a ramus communicans to the ophthalmic division of the trigeminal nerve and

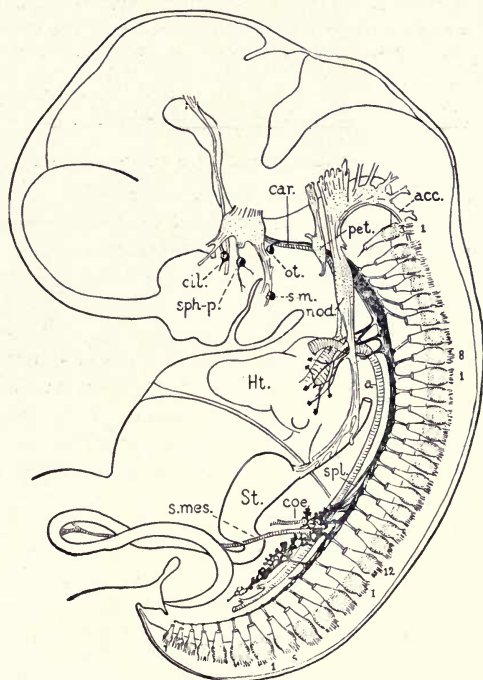


FIG. 366.—The sympathetic system in a 16 mm. human embryo (Streeter in Lewis and Stöhr). $\times 7$. The ganglionated trunk is heavily shaded. The first and last cervical, thoracic, lumbar, sacral and coccygeal spinal ganglia are numbered. *a.*, Aorta; *acc.*, accessory nerve; *car.*, carotid artery; *cil.*, ciliary ganglion; *coe.*, coeliac artery; *Ht.*, heart; *nod.*, nodose ganglion; *ot.*, otic ganglion; *pet.*, petrosal ganglion; *s-m.*, submaxillary ganglion; *s.mes.*, superior mesenteric artery; *sph-p.*, spheno-palatine ganglion; *spl.*, splanchnic nerve; *St.*, stomach.

receives fibers from the oculomotor nerve. Its cells are apparently derived entirely from the semilunar ganglion. The *spheno-palatine*, *submaxillary*, and *otic ganglia* probably take their origin from migrating cells of the semilunar ganglion, but as they are connected with the geniculate ganglion of the facial nerve it is possible that the latter contributes to their formation also. The *spheno-palatine ganglion* is connected directly

with the semilunar ganglion by two communicating rami. The *submaxillary ganglion* is intimately related through the mandibular division of the trigeminal nerve to the semilunar ganglion, while the *otic ganglion* is united to the latter by a plexus and is related to the glossopharyngeal nerve through its tympanic branch.

The *cervical ganglia* lose their segmental arrangement and represent the fusion of from two to five ganglia of the cervical and upper thoracic region. The more distally located *prevertebral ganglia* (of the cardiac, coeliac, hypogastric, and pelvic plexuses) are derived from cells of the neural crest which migrate to a greater distance ventrally (Fig. 366). The *visceral ganglia* (of the myenteric and submucous plexuses, and the prevertebral cardiac plexus as well, are derived by Kuntz chiefly from migratory cells from the hind-brain and from the vagus ganglia.

The sympathetic nerve cells give rise to axons and dendrites, and are thus typically multipolar cells. Their axons possess a neurilemma sheath, but remain unmyelinated.

D. THE CHROMAFFIN BODIES AND SUPRARENAL GLAND

Certain cells of the sympathetic ganglia, instead of becoming neurons, are transformed into peculiar gland cells; these produce an important internal secretion which affects the blood pressure. The secretion formed by these cells causes them to stain brown when treated with chrome salts, hence they are called *chromaffin cells*. Cells of this type, derived from the ganglionated cord of the sympathetic system, give rise to structures known as *chromaffin bodies*. Chromaffin derivatives of the coeliac plexus, together with mesenchymal tissue, also form the anlage of the *suprarenal gland*.

The **Chromaffin Bodies** of the ganglionated cords are rounded, cellular masses partly embedded in the dorsal surfaces of the ganglia (Fig. 367). At birth they may attain a diameter of 1 to 1.5 mm. In number they vary from one to several for each ganglion.

Similar chromaffin bodies may occur in all the larger sympathetic plexuses. The largest of these structures, found in the abdominal sympathetic plexuses, are the *aortic chromaffin bodies* (of Zuckerkandl). These occur on either side of the inferior mesenteric artery, ventral to the aorta and mesial to the metanephros. At birth they attain a length of 9 to 12 mm. and are composed of cords of chromaffin cells intermingled with strands of connective tissue, the whole being surrounded by a connective-tissue capsule. After birth the chromaffin bodies degenerate, but do not disappear entirely.

The Glomus Caroticum.—Associated with the intercarotid sympathetic plexus is a highly vascular chromaffin body known as the *carotid gland*. Its anlage has been first observed in 20 mm. embryos.

The **Suprarenal Gland** is developed from chromaffin tissue, which become its medulla, and from mesodermal tissue that give rise to its cortex. In an embryo of 6 mm. the anlage of the cortex begins to form from ingrowing buds of the peritoneal mesothelium. At about 9 mm. the glands are

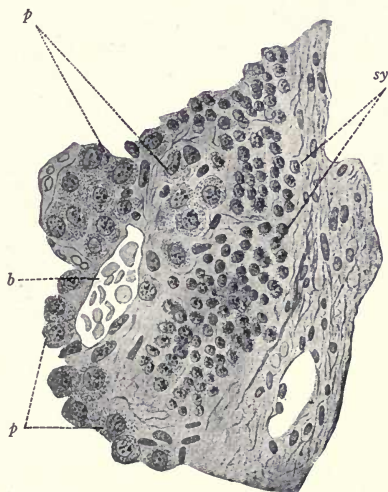


FIG. 367.—Section through a chromaffin body in a 44 mm. human fetus (after Kohn). $\times 450$.
p, Mother chromaffin cells; sy, sympathetic cells; b, blood vessel.

definite organs and their vascular structure is evident (Fig 201). The cellular elements of the cortex are at first larger than the chromaffin cells that give rise to the medulla. The anlagen of the glands early project from the dorsal wall of the coelom between the mesonephros and mesentery; here they become relatively huge organs (Figs. 221, 232 and 233). The differentiation of the cortex into its three characteristic layers is not completed until between the second and third years. The inner *reticular zone* is formed first, next the *fasciculate zone*, and last the *glomerular zone* (50 mm.).

The chromaffin cells of the medulla are derived from the coeliac plexus of the sympathetic system. In embryos of 15 to 19 mm. (Fig. 368), masses of these cells begin to migrate from the median side of the suprarenal anlage to a central position, and later surround the central vein

which is present in embryos of 23 mm. The primitive chromaffin cells are small and stain intensely. They continue their immigration until after birth.

Anomalies.—Portions of the suprarenal anlage may be separated from the parent gland and form *accessory suprarenals*. As a rule, such accessory glands are composed only of cortical substance; they may migrate some distance from their original position, accompanying the genital glands. In fishes the cortex and medulla persist normally as separate organs.



FIG. 368.—Transverse section through the right suprarenal gland of a 15.5 mm. human embryo (after Bryce). *sy*, *sy'*, Groups of chromaffin sympathetic cells migrating into the gland.

E. DEVELOPMENT OF THE SENSE ORGANS

The sense cells of primitive animals, such as worms, are ectodermal in origin and position. Only those of the vertebrate olfactory organ have retained this primitive relation. During phylogeny the cell-bodies of all other such primary sensory neurones migrated inward to form the dorsal ganglion (Parker), hence their peripheral processes either end freely in the epithelium or appropriate new cells to serve as sensory receptors (taste; hearing).

The nervous structures of the sense organs consist of the general sense organs of the integument, muscles, tendons, and viscera, and of the special sense organs, which include the taste buds of the tongue, the olfactory epithelium, the retina of the eye, and the epithelial lining of the ear labyrinth.

I. GENERAL SENSORY ORGANS

Free nerve terminations form the great majority of all the general sensory organs. When no sensory corpuscle is developed, the neurofibrils of the sensory nerve fibers separate and end among the cells of the epithelia.

Lamellated corpuscles first arise during the fifth month as masses of mesodermal cells clustered around a nerve termination. These cells increase in number, flatten out, and give rise to the concentric lamellæ of these peculiar structures. In the cat these corpuscles increase in number by budding.

The *tactile corpuscles*, according to Ranvier, are developed from mesenchymal cells and branching nerve fibrils during the first six months after birth.

II. TASTE BUDS

The anlagen of the taste buds appear as thickenings of the lingual epithelium in three month fetuses. The cells of the taste bud anlage lengthen and later extend to the surface of the epithelium. They are differentiated into the sensory *taste cells*, with modified cuticular tips, and into *supporting cells*. The taste buds are supplied by nerve fibers of the seventh, ninth, and tenth cerebral nerves; the fibers branch and end in contact with the periphery of the taste cells.

In the fetus of five to seven months, taste buds are more widely distributed than in the adult. They are found in the walls of the vallate, fungiform, and foliate papillæ of the tongue, on the under surface of the tongue, on both surfaces of the epiglottis, on the palatine tonsils and arches, and on the soft palate. After birth many of the taste buds degenerate, only those on the lateral walls of the vallate and foliate papillæ, on a few fungiform papillæ, and on the laryngeal surface of the epiglottis persisting.

III. THE OLFACTORY ORGAN

The olfactory epithelium arises as paired thickenings or *placodes* of the cranial ectoderm (Fig. 369 A). The placodes are depressed to form the *olfactory pits*, or *fossæ*, about which the nose develops (Fig. 89).

In embryos of 4 to 5 mm. (Fig. 369) the placodes are sharply marked off from the surrounding ectoderm as ventro-lateral thickenings near the top of the head. They are flattened and begin to invaginate in embryos

of 6 to 7 mm. In 8 mm. embryos the invagination has produced a distinct *fossa*, surrounded everywhere, save ventrally, by a marginal swelling.

The later development of the olfactory organ is associated with that of the face. It will be remembered (p. 146) that each first branchial arch forks into a maxillary and mandibular process. Dorsal to the oral cavity is the fronto-nasal process of the head, lateral to it the maxillary processes, and ventral to it are the mandibular processes (Fig. 97). With

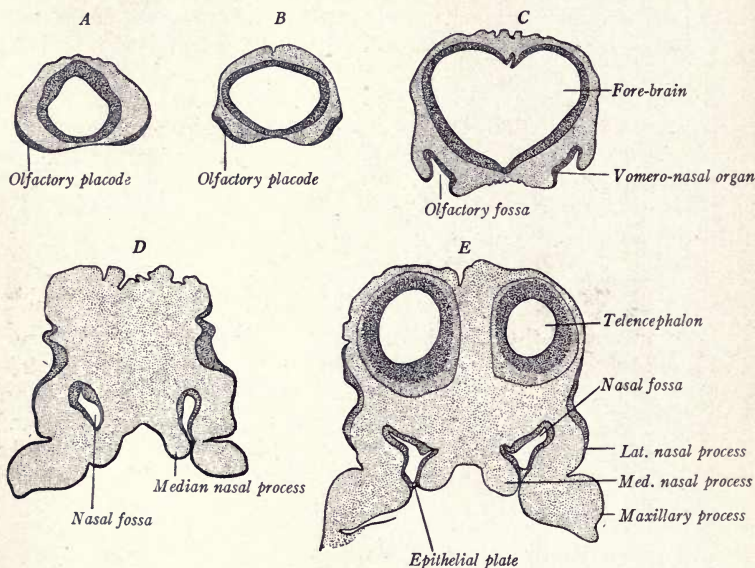


FIG. 369.—Sections through the olfactory anlagen of human embryos. A, 4.9 mm. ($\times 20$); B, 6.5 mm. ($\times 13$); C, 8.8 mm. ($\times 13$); D and E, 10 mm. (A, B and C from Keibel and Elze).

the development of the nasal pits, the fronto-nasal process is divided into paired *lateral nasal processes* and a single *median frontal process*, from which are differentiated later the *median nasal processes*, or *processus globulares* (Fig. 370). The nasal pits are at first grooves, each bounded mesially by the median frontal process and laterally by the lateral nasal process and the maxillary process (Fig. 370 A). The fusion of the maxillary processes with the ventro-lateral ends of the median frontal process converts the nasal grooves into blind pits, or fossæ, shutting them off from the mouth cavity (Fig. 370). Thus, in embryos of 10 to 12 mm. the nasal fossa has but one opening, the *external naris*, and is separated from the mouth cavity by an ectodermal plate (Fig. 369 D, E).

When the ventro-lateral ends of the median frontal process enlarge and become the median nasal processes they fuse with the lateral nasal processes and reduce the size of the external nares (Fig. 370 *B*). Externally, the nares are now bounded ventrally by the fused nasal processes. The epithelial plates which separate the nasal fossæ from the primitive mouth cavity become thin, membranous structures caudally, and, rupturing, produce two internal nasal openings, the *primitive choanæ* (Fig. 153). Cranially, the epithelial plate is split by ingrowing mesoderm of the maxillary process and median nasal process which replaces it, thereby forming the *primitive palate* (Fig. 369 *D*). The primitive palate forms the *lip* and

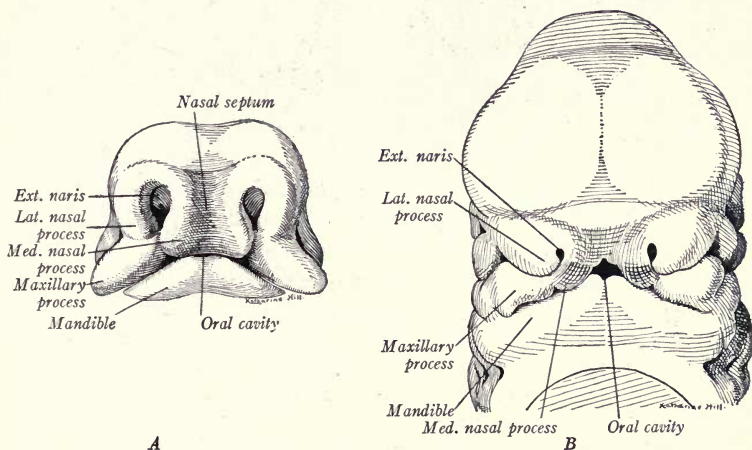


FIG. 370.—Two stages in the development of the jaws and nose. *A*, Ventral view of the end of the head of a 10.5 mm. human embryo (after Peter); *B*, of an 11.3 embryo (after Rabl).

the *premaxillary palate*. The nasal fossæ now open externally through the external nares and internally into the roof of the mouth cavity through the primitive choanæ.

Coincident with these changes, the median frontal process has become relatively smaller, and that portion of it between the external nares and the nasal fossæ forms the *nasal septum* (Fig. 370). As the facial region grows and elongates, the primitive choanæ becomes longer and form slit-like openings in the roof of the mouth cavity. By the development and fusion of the palatine processes (described on p. 148) the dorsal portion of the mouth cavity is separated off and constitutes the nasal passages (cf. Figs. 371 and 372). The nasal passages of the two sides for a time communicate through the space between the hard palate and the nasal

septum. Later, the ventral border of the septum fuses with the hard palate and completely separates the nasal passages (Fig. 372). The nasal passages of the adult thus consist of the primitive nasal fossæ plus a portion of the primitive mouth cavity which has been appropriated secondarily by the development of the hard palate. The passages of the adult thus open caudally by secondary *choanae* into the cavity of the pharynx.

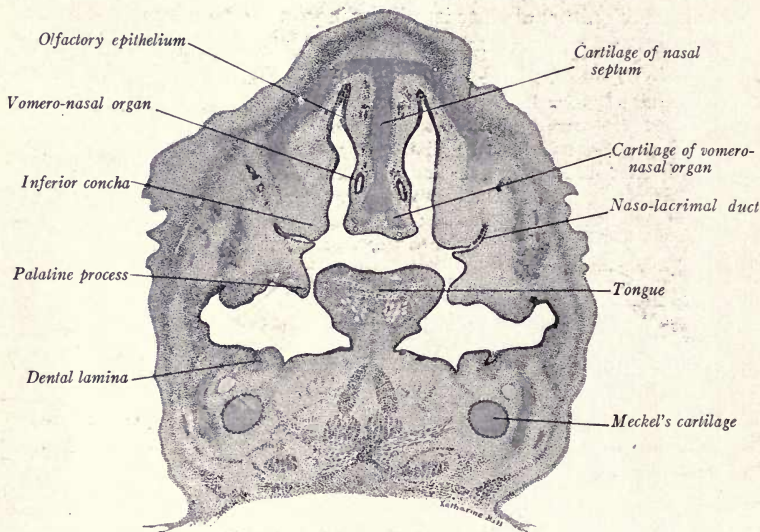


FIG. 371.—Transverse section through the nasal passages and palatine processes of a 20 mm. human embryo. In the nasal septum is a section of the vomero-nasal organ (of Jacobson). $\times 30$.

Part of the epithelium which lines the nasal fossæ is transformed into the sensory olfactory epithelium (Fig. 371). The remainder covers the conchæ and lines the vomero-nasal organ (of Jacobson), the ethmoidal cells, and the cranial sinuses.

The **Vomero-nasal Organ** (of Jacobson) is a rudimentary epithelial structure which first appears in 8.5 to 9 mm. embryos on the median wall of the nasal fossa (Fig. 369 C, E). The groove deepens and closes caudally to form a tubular structure in the cranial portion of the nasal septum (Fig. 371). During the sixth month it attains a length of 4 mm. Nerve fibers, arising from cells in its epithelium, join the olfactory nerve, and it also receives fibers from the *n. terminalis*. In late fetal stages it often degenerates, but may persist in the adult (Merkel, Mangakis). Special

cartilages are developed for its support (Fig. 371). The organ of Jacobson is not functional in man, but in many animals evidently constitutes a special olfactory organ.

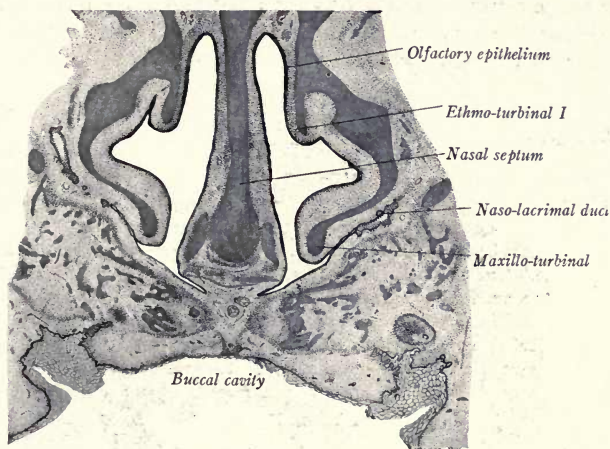


FIG. 372.—Transverse section through the nasal passages of a 65 mm. human fetus. $\times 14$.

The **Conchæ** are structures which are poorly developed in man. They appear on the lateral and median walls of the primitive nasal fossæ. The *inferior concha*, or *maxillo-turbinal*, is developed first in human

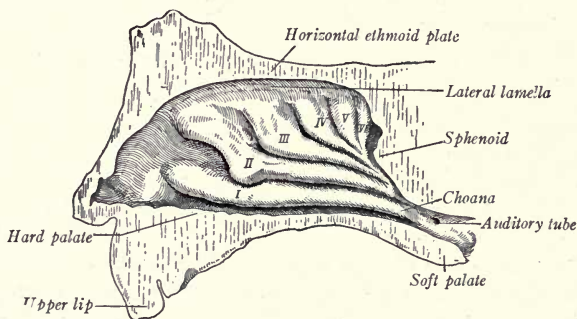


FIG. 373.—Right nasal passage of a fetus at term (after Killian). *I*, Maxillo-turbinal; *II-VI*, ethmo-turbinals. The slight elevation at the left of *I* and *II* is the naso-turbinal.

embryos (Figs. 371 and 372). It forms a ridge along the caudal two-thirds of the lateral wall and is marked off by a ventral groove which becomes the *inferior nasal meatus* (Fig. 373). The *naso-turbinal* is very

rudimentary and appears as a slight elevation dorsal and cranial to the *inferior concha* (Fig. 373). Dorsal to the inferior concha arise five *ethmo-turbinals*, which grow progressively smaller caudally. According to Peter, the ethmo-turbinals arise on the medial wall of the nasal fossa, and, by a process of unequal growth, are transferred to the lateral wall (Fig. 372). Accessory conchæ are also developed (Killian).

In adult anatomy, the *inferior concha* forms from *I* (Fig. 373), the *middle concha* from *II*, and the *superior concha* from *III* and *IV*.

In addition to the ridges formed by the conchæ, there are developed in the grooves between the ethmo-turbinals the *ethmoidal cells*. After birth the frontal recess (located between *I* and *II*, Fig. 373) gives rise to the *frontal sinus*. During the third month the *maxillary sinus* grows out from the inferior recess of the same groove. The most caudal end of the nasal fossa becomes the *sphenoidal sinus*, which, as it increases in size, invades the sphenoid bone. These cells and sinuses form as excavations of the bone which become lined with simultaneously advancing epithelial evaginations.

The cells of the olfactory epithelium acquire cilia, but only a small area, representing the primitive epithelial invagination, functions as an olfactory sense organ. The olfactory cells of this area give rise to the fibers which constitute the olfactory nerve (cf. p. 357).

IV. THE EYE

The anlage of the human eye appears in embryos of 2.5 mm. as a thickening and evagination of the neural plate of the fore-brain. At this stage the neural groove of the fore-brain has not closed (Figs. 324, 330 and 382). At 4 mm. the *optic vesicles* are larger, but still may be connected by a wide opening with the brain cavity (Fig. 374 *A, B*). In the section shown in Fig. 374 *C*, the optic vesicle is attached to the ventral brain wall by a distinct *optic stalk* (cf. Fig. 343).

The thickening, flattening, and invagination of the distal and ventral wall of the optic vesicle gives rise to the *optic cup* (Fig. 374 *B-D*). The area of invagination also extends ventrally along the optic stalk and produces a groove known as the *chorioid fissure* (Figs. 331, 375 and 377). At the same time that the optic vesicle is converted into the optic cup, the ectoderm overlying the vesicle thickens, as seen in Fig. 374 *B*, forming the *lens plate*, or *optic placode*. This plate invaginates to form the *lens pit*, the external opening of which closes in embryos of 6 to 7 mm. (Fig. 374 *D*), producing the *lens vesicle*, which at first remains attached to the overlying ectoderm.

The invagination of the optic vesicle is a self-governed process. On the contrary, contact of the optic vesicle with the overlying ectoderm stimulates the latter to lens formation, even in regions that normally never differentiate a lens (Lewis, 1907). It is possible, however, for a lens to arise independently of this contact stimulus (Stockard, 1910).

In an embryo of 10 mm. (Fig. 376) the essential plan of the eye is foreshadowed. The lens vesicle has separated from the ectoderm, which will form the epithelium of the cornea. The lens vesicle in earlier stages

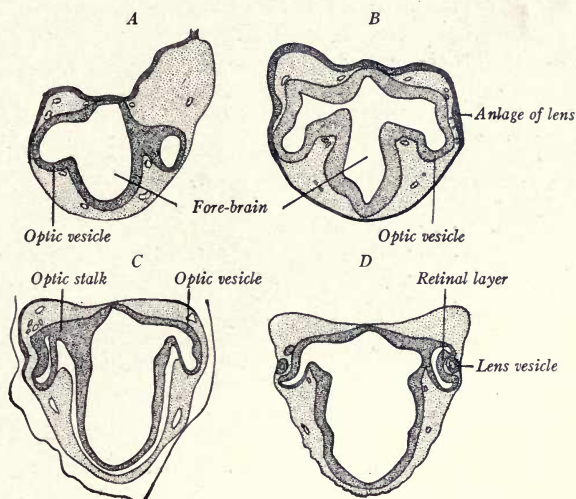


FIG. 374.—Stages in the early development of the human eye. A, B, 4 mm. ($\times 27$); C, 5 mm. ($\times 23$); D, 6.25 mm. ($\times 18$); (after Keibel and Elze).

(Fig. 374 D) is closely applied to the inner wall of the optic cup, but now it has separated from it, leaving a space in which the *vitreous body* develops. The inner *retinal layer* of the optic cup has become very thick

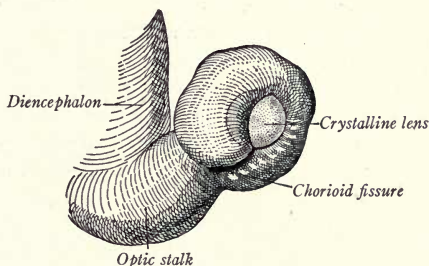


FIG. 375.—The optic stalk, cup and lens of a human embryo of 12.5 mm. The chorioid fissure has not yet extended along the optic stalk (from Fuchs, after Hochstetter). $\times 90$.

and is applied to the outer layer, so that the cavity of the primitive optic vesicle is nearly obliterated (Fig. 376). Pigment granules have begun to appear in the outer layer of cells to form the *pigment layer* of the retina.

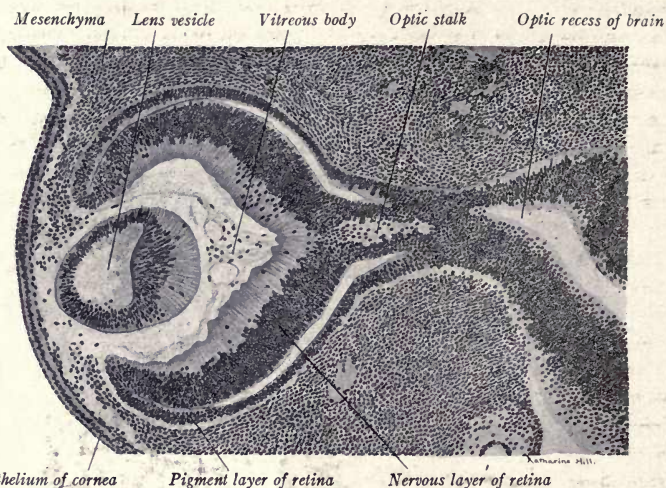


FIG. 376.—A transverse section through the optic cup, stalk and lens of a 10 mm. human embryo. $\times 100$.

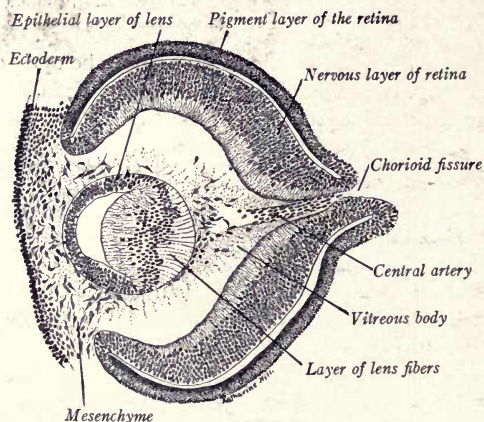


FIG. 377.—Transverse section passing through the optic cup at the level of the chorioid fissure. The central artery of the retina is seen entering the fissure and sending a branch to the proximal surface of the lens; from a 12.5 mm. human embryo. $\times 105$.

Mesenchymal tissue surrounds the optic cup and is beginning to make its way between the lens vesicle and the ectoderm. Here, the *anterior chamber* of the eye develops later as a cleft in the mesoderm. The distal mesenchymal tissue (next the ectoderm) forms the *substantia propria* of the *cornea* and its posterior epithelium; while the proximal mesenchyma (next the lens) differentiates into the *vascular capsule* of the lens. The mesenchyme surrounding the optic cup is continuous with that which forms the cornea; later it gives rise to the sclerotic layer, to the chorioid layer, and to the anterior layers of the ciliary body and iris.

Both the inner and outer layers of the optic cup are continued into the optic stalk, as seen in Fig. 376. This is due to the trough-like invagination of the ventral wall of the optic stalk, the *chorioid fissure*, when the optic vesicle is transformed into the optic cup (Fig. 375). Into the chorioid fissure grows the *central artery* of the retina, carrying with it into the posterior cavity of the eye a small amount of mesenchyme (Fig. 377). Branches from this vessel extend to the posterior surface of the lens and supply it with nutriment for its growth. At a later stage the chorioid fissure closes, so that the distal rim of the optic cup forms a complete circle.

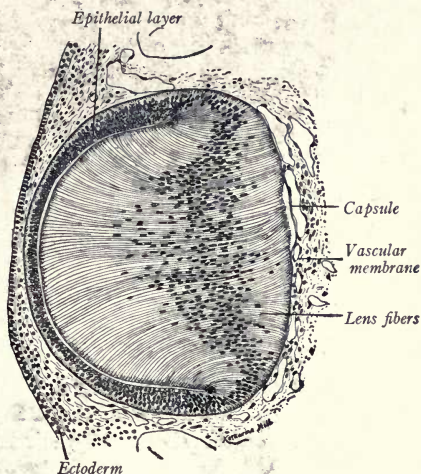


FIG. 378.—Section through the lens and corneal ectoderm of a 16 mm. pig embryo. $\times 140$.

The *lens vesicle*, and its early development from the ectoderm, have been described. Its proximal wall is much thickened in 10 mm. embryos (Fig. 376), and these cells form the *lens fibers* which will soon obliterate the cavity of the vesicle, as in embryos of 15 to 17 mm. (Fig. 378). The cells of the distal layer remain of a low columnar type and constitute the epithelial layer of the lens. When the lens fibers attain a length of 0.18 mm. they cease forming new fibers by cell division. New fibers thereafter arise from the cells of the epithelial layer at its equatorial line of union with the lens fibers. The nuclei are arranged in a layer, convex toward the outer surface of the eye, but they later degenerate, the degeneration beginning centrally. Lens sutures are formed on the proximal and distal faces of the lens when the longer, newly formed,

peripheral fibers overlap the ends of the shorter, central fibers. By an intricate but orderly arrangement of fibers these sutures are later transformed into *lens-stars* of three, and finally of six or nine rays (Fig. 379). The structureless capsule of the lens is probably derived from the lens cells. The lens, at first somewhat triangular in cross section, becomes nearly spherical at three months (Fig. 379).

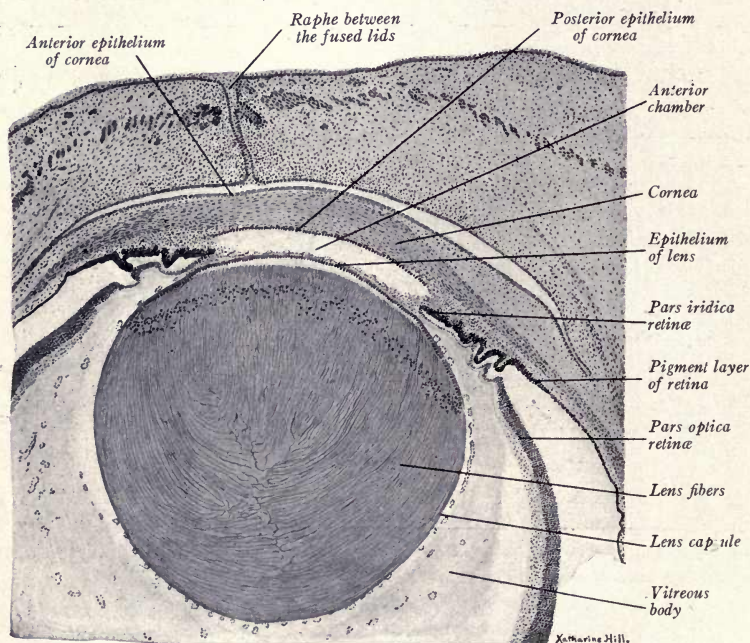


FIG. 379.—Section through the distal half of the eyeball and eyelids of a 65 mm. human fetus.
× 35.

The origin of the **vitreous body**, whether ectodermal or mesodermal, has long been in doubt. Modern evidence apparently points to its derivation from both sources.

It is certain that vitreous tissue is formed before mesenchyma is present in the cavity of the optic cup. Szily (1908) regards this primitive vitreous body as a derivative of both retinal and lens cells, it forming a non-cellular network of cytoplasmic processes which are continuous with the cells of the lens and retina. With the ingrowth of the central artery of the retina, from which the artery of the lens passes to the proximal surface of the lens and branches on it, a certain amount of mesenchymal tissue invades the optic cup, and this tissue probably contributes to the development of the vitreous body (Fig. 377).

The mesenchyma accompanying the vessels to the proximal surface of the lens, and that on its distal surface, give rise to the vascular *capsule* of the lens (Fig. 377). On the distal surface of the lens this is supplied by branches of the anterior ciliary arteries and is known as the *pupillary membrane*; the vessels disappear and the membrane degenerates just before birth. The artery of the lens also degenerates, its wall persisting as the transparent *hyaloid canal*. Fibrillæ extending in the vitreous humor from the pars ciliata of the retinal layer to the capsule of the lens persist as the *zonula ciliaris*, or *suspensory ligament* of the lens.

Differentiation of the Optic Cup.—We have seen that of the two layers of the optic cup, the outer becomes the *pigment layer* of the *retina*. Pigment granules appear in its cells in embryos of 7 mm. and the pigmentation of this layer is marked in 12 mm. embryos (Fig. 377).

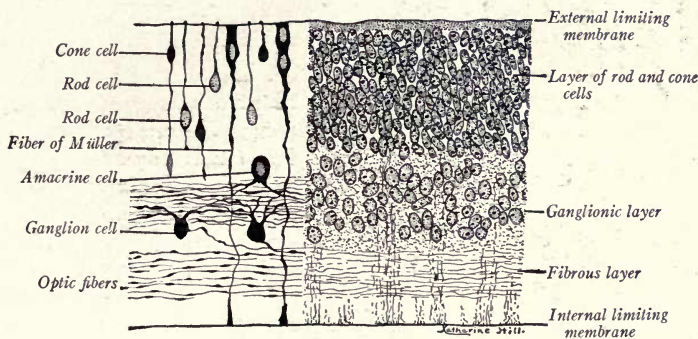


FIG. 380.—Section of the nervous layer of the retina from a 65 mm. human fetus. At the left is shown diagrammatically the cellular elements of the retina according to Cajal. $\times 440$.

The inner, thicker layer of the optic cup, the *retinal layer* proper, is subdivided into a distal zone, the *pars cæca*, which is non-nervous, and into the *pars optica*, or the true nervous portion. The line of demarcation between the pars optica and the pars cæca is a serrated circle, the *ora serrata*. By the development of the ciliary bodies the blind portion of the retinal layer, the pars cæca, is differentiated into a *pars ciliaris* and *pars iridica retinæ*. The former, with a corresponding zone of the pigment layer, covers the ciliary bodies. The *pars iridica* forms the proximal layer of the *iris* and blends intimately with the pigment layer in this region, its cells also becoming heavily pigmented (Fig. 379).

The *pars optica*, or nervous portion of the retina, begins to differentiate proximally and the differentiation extends distally. An outer *cellular layer* and an inner *fibrous layer* may be distinguished in 12 mm. embryos

(Fig. 377). These correspond to the cellular layer (ependymal and mantle zones) and marginal layer of the neural tube. In fetuses of 65 mm. (C R) the retina shows three layers, large ganglion cells having migrated in from the outer cellular layer of rods and cones (Fig. 380). In a fetus of the seventh month all the layers of the adult retina may be recognized (Fig. 381). As in the wall of the neural tube, there are differentiated in the retina supporting tissue and nervous tissue. The supporting elements, or *fibers of Müller*, resemble ependymal cells and are radially arranged

(Figs. 380 and 381). Their terminations form *internal and external limiting membranes*.

The neuroblasts of the retina differentiate into an outer layer of *rod and cone cells*, the visual cells of the retina, which are at first unipolar (Fig. 381). Internal to this layer are layers of bipolar and multipolar cells. The inner layer of multipolar cells constitutes the *ganglion cell layer*. Axons from these cells form the inner *nerve fiber layer* of optic fibers. These converge to the optic stalk, and, in embryos of 15 mm. grow

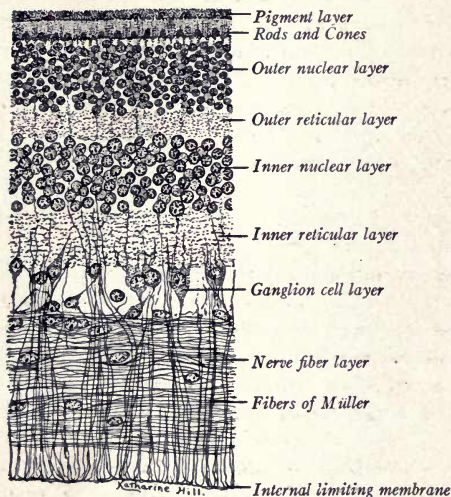


FIG. 381.—Section through the pars optica of the retina from a seven months' fetus. $\times 440$.

back in its wall to the brain. The cells of the optic stalk are converted into neuroglia supporting tissue and the cavity in the stalk is gradually obliterated. The optic stalk is thus transformed into the *optic nerve* (cf. p. 358).

The Sclerotic and Chorioid Layers, and their Derivatives.—After the mesenchyme grows in between the ectoderm and the lens (Fig. 377), the lens and optic cup are surrounded by a condensed layer of mesenchymal tissue, which gives rise to the supporting and vascular layers of the eyeball. By condensation and differentiation of its outer layers, a dense layer of white fibrous tissue is developed, which forms the *sclera*. This corresponds to the dura mater of the brain. In the mesenchyme of 25 mm. embryos, a cavity appears distally which separates the condensed layer of mesenchyme, continuous with the sclerotic, from the vascular capsule of

the lens (Fig. 379). This cavity is the *anterior chamber* of the eye and separates the anlage of the *cornea* from the lens capsule.

An inner layer of mesenchyme, between the anlage of the sclerotic and the pigment layer of the retina, becomes highly vascular during the sixth month. Its cells become stellate in form and pigmented, so that the tissue is loose and reticulate. This vascular tissue constitutes the *chorioid layer*, in which course the chief vessels of the eye. The chorioid layer corresponds to the pia mater of the brain. Distal to the ora serrata of the retinal layer, the chorioid is differentiated into: (1) the vascular folds of the *ciliary bodies*; (2) the smooth fibers of the *ciliary muscle*; (3) the stroma of the *iris*. The proximal pigmented layers of the iris are derived from the pars iridica retinae and from a corresponding zone of the pigment layer. Of these, the pigment layer cells give rise to the *sphincter* and *dilator muscles* of the iris. These smooth muscle fibers are thus of ectodermal origin.

The **Eyelids** appear as folds of the integument in 20 mm. embryos. The lids come together and the epidermis at their edges is fused in 33 mm. embryos (Fig. 379). Later, when the epidermal cells are cornified, separation of the eyelids takes place. A third, rudimentary eyelid, corresponding to the functional nictitating membrane of lower vertebrates, forms the *plica semilunaris*. The epidermis of the eyelids forms a continuous layer on the inner surfaces, known as the *conjunctiva*, which in turn is continuous with the anterior epithelium of the cornea.

The **Eyelashes**, or *cilia*, develop like ordinary hairs and are provided with small sebaceous glands. In the *tarsus*, or dense connective-tissue layer of the eyelids, which lies close to the conjunctival epithelium, there are developed about 30 *tarsal* (Meibomian) *glands*. These arise as ingrowths of the epithelium at the edges of the eyelids, while the latter are still fused.

The **Lacrimal Glands** appear in embryos of about 25 mm., according to Keibel and Elze. They arise as five or six ingrowths of the conjunctiva, dorsally and near the external angle of the eye. The anlagen are at first knob-like, but rapidly lengthen into solid epithelial cords. They begin to branch in 30 mm. embryos. At stages between 50 and 60 mm. (C R), additional anlagen appear which also branch.

In 38 mm. (C R) embryos, a septum begins to partition the gland into orbital and palpebral portions. This septum is complete at 60 mm. (C R), the five or six anlagen first developed constituting the peripheral orbital part. Lumina appear in the glandular cords in fetuses of 50 mm. (C R) by the degeneration of the central cells. Accessory lacrimal glands appear a month before term. The lacrimal gland is not fully differentiated at birth, being only one-third the size of the adult gland. In old age marked degeneration occurs.

The **Naso-lacrimal Duct** arises in 12 mm. embryos as a ridge-like thickening of the epithelial lining of the naso-lacrimal groove (Fig. 149).

which, it will be remembered, extends from the inner angle of the eye to the olfactory fossa. This thickening becomes cut off, and, as a solid cord, sinks into the underlying mesoderm (Schaeffer). Secondary sprouts, growing out from this cord to the eyelids, form the *lacrimal canals*. A lumen, completed at birth, appears during the third month (Fig. 372).

Anomalies.—Lack of pigment in the retina and iris is usually associated with general albinism. If the chorioid fissure fails to close properly, there results a gaping, and hence unpigmented, defect, or *coloboma*, in the iris, ciliary body, or chorioid. In *cyclopia*, a single median eye replaces the usual paired condition. All intergrades exist from closely approximated, separate eyes to perfect unity. The mode of genesis, whether from the fusion of separate eyes or from the inhibited separation of a common anlage into its bilateral derivatives, is in dispute. In cases of cyclopia the nose is usually a cylindrical proboscis, situated above the median eye.

V. THE EAR

The human ear consists of a sound-conducting apparatus and of a receptive organ. The conveyance of sound is the function of the *external* and *middle ears*. The end organ proper is the *inner ear*, with the auditory

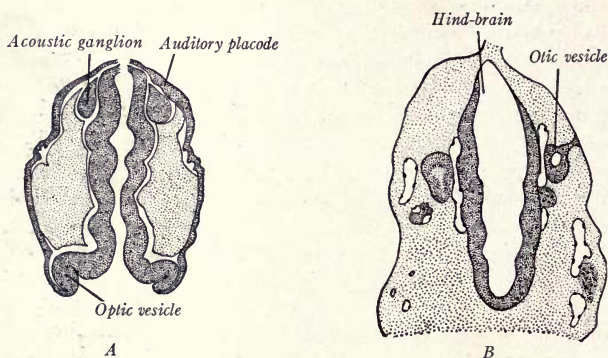


FIG. 382.—Two stages in the early development of the internal ear (after Keibel and Elze). A, Horizontal section through the open neural tube of a 2 mm. human embryo, ($\times 27$); B, through the hind-brain of a 4 mm. human embryo ($\times 33$).

apparatus residing in the *cochlear duct*. Besides this acoustic function the labyrinthine portion of the inner ear acts as an organ of equilibration.

The Inner Ear.—The epithelium of the internal ear is derived from the ectoderm. Its first anlage appears in embryos of 2 mm. as a thickened ectodermal plate, the *auditory placode* (Fig. 382 A). These are developed, dorsal to the second branchial grooves, at the sides of the hind-brain opposite the fifth neuromeres (Fig. 383). The placodes are invaginated

to form hollow vesicles which close in the embryos of 2.5 to 3 mm., but remain temporarily attached to the ectoderm (Fig. 382 B).

The *auditory vesicle*, or *otocyst*, when closed and detached, is nearly spherical, but approximately at the point where it was attached to the

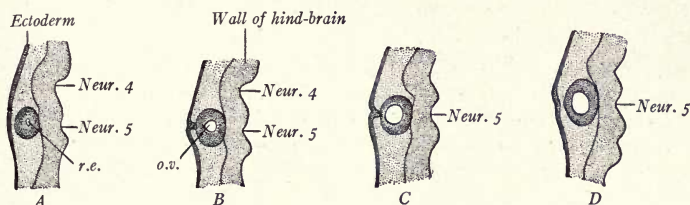


FIG. 383.—Four sections through the right otic vesicle of a 4 mm. human embryo (after Keibel and Elze). \times about 30. *r.e.*, Endolymphatic recess; *o.v.*, otic vesicle; *Neur.* 4, *Neur.* 5, neuromeres.

ectoderm a recess, the *ductus endolymphaticus*, is formed. The point of origin of this recess is shifted later from a dorsal to a mesial position (Figs. 384 and 385 a). The endolymph duct corresponds to that of selachian fishes, which remains permanently open to the exterior. In man, its extremity is closed and dilated to form the *endolymph sac* (Fig. 385 f).

In an embryo of about 7 mm. the vesicle has elongated, its narrower ventral process constituting the anlage of the *cochlear duct* (Fig. 385 a). The wider, dorsal portion of the otocyst is the *vestibular anlage*, which shows indications dorsally of the developing semicircular canals. These are formed in 11 mm. embryos as two

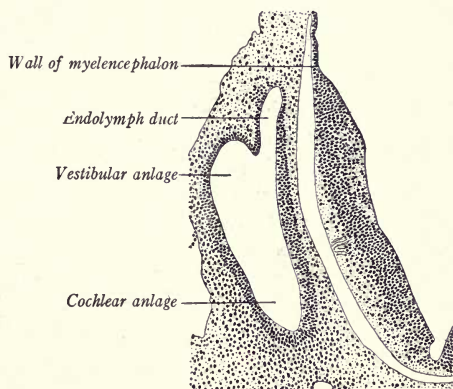


FIG. 384.—Right half of a transverse section through the hind-brain and otic vesicles, showing the position of the endolymph duct. From a 6.9 mm. human embryo (His).

pouches—the anterior and posterior canals from a single pouch at the dorsal border of the otocyst, the lateral canal later from a lateral out-pocketing (Fig. 385 c). Centrally, the walls of these pouches flatten and fuse to form epithelial plates. In the three plates thus produced canals are left peripherally, communicating with the cavity of the vestibule.

Soon, the epithelial plates are resorbed, leaving the semicircular canals as in Fig. 385 *d, e*. Dorsally, a notch separates the anterior and posterior canals. Of these canals, the anterior is completed before the posterior. The lateral canal is the last to develop.

In a 20 mm. embryo (Fig. 385 *e*) the three canals are present and the cochlear duct has begun to coil like a snail shell. It will be seen that the anterior and posterior canals have a common opening dorsally into the vestibule, while their opposite ends, and the cranial end of the lateral canal, are dilated to form *ampullæ*. In each ampulla is located an end organ, the *crista ampullaris*, which will be referred to later. By a constriction of its wall the vestibule is differentiated into a dorsal portion, the *utricle*, to which are attached the semicircular canals, and a ventral portion, the *sacculus*, connected with the cochlear duct (Fig. 385 *e, f*). At 30 mm. the adult condition is nearly attained. The sacculus and utricle are more completely separated, the canals are relatively longer, their ampullæ more prominent, and the cochlear duct is coiled about two and a half turns (Fig. 385 *f*). In the adult, the sacculus and utricle become completely separated from each other, but each remains attached to the endolymph duct by a slender canal that represents the prolongation of their respective walls. Similarly, the cochlear duct is constricted from the sacculus, the basal end of the former becomes a blind process, and a canal, the *ductus reuniens*, alone connects the two.

The epithelium of the labyrinth at first is composed of a single layer of low columnar cells. At an early stage, fibers from the acoustic nerve grow between the epithelial cells in certain regions and these become modified to produce special sense organs. These end organs are the *cristæ ampullares* in the ampullæ of the semicircular canals, the *maculæ acusticæ* in the utricle and sacculus, and the *spiral organ* (of Corti) in the cochlear duct.

The *cristæ* and *maculæ* are static organs, or sense organs for maintaining equilibrium. In each ampulla, transverse to the long axis of the canal, the epithelium and underlying tissue form a curved ridge, the *crista*. The cells of the epithelium are differentiated into: (1) *sense cells*, with bristle-like hairs at their ends; and (2) *supporting cells*. About the bases of the sensory cells branch nerve fibers from the vestibular division of the acoustic nerve. The *maculæ* resemble the *cristæ* in their development save that larger areas of the epithelium are differentiated into cushion-like end organs. Over the *maculæ*, concretions of lime salts may form *otoconia* which remain attached to the sensory bristles.

The true organ of hearing, the *spiral organ*, is developed in the *basal epithelium* of the cochlear duct, basal having reference here to the base of the cochlea. The development of the spiral organ has been studied carefully only in the lower mammals. According to Prentiss (1913), in

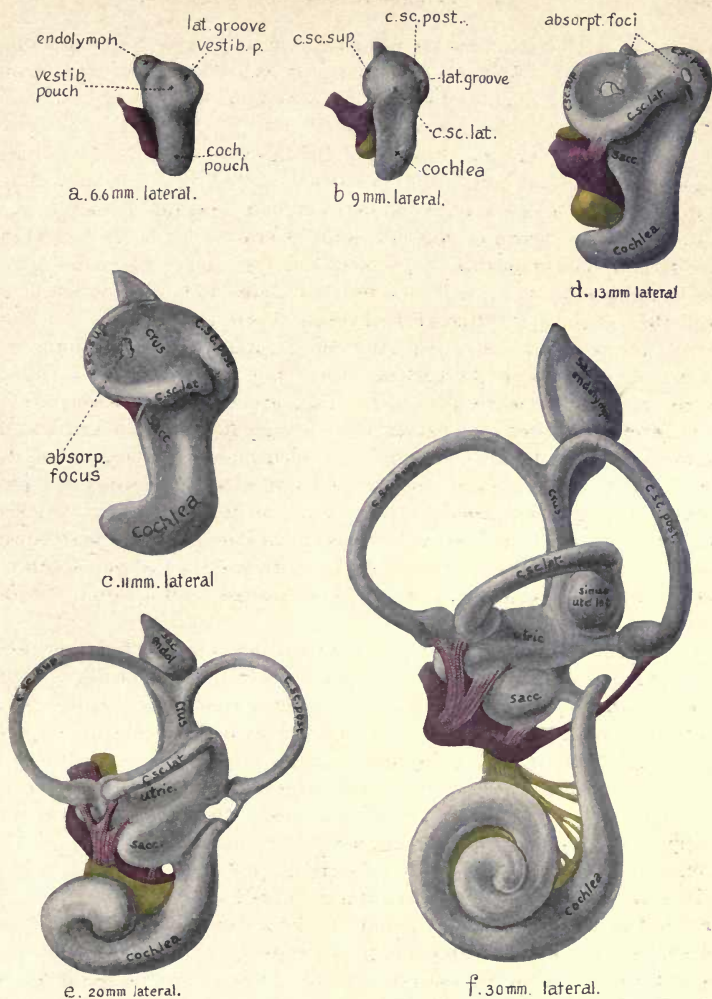


FIG. 385.—Six stages in the development of the internal ear (Streeter). $\times 25$. The figures show lateral views of models of the left membranous labyrinth—*a* at 6.6 mm.; *b*, at 9 mm.; *c* at 11 mm.; *d* at 13 mm.; *e* at 20 mm.; and *f* at 30 mm. The colors yellow and red are used to indicate respectively the cochlear and vestibular divisions of the acoustic nerve and its ganglia. *absorp. focus*, Area of wall where absorption is complete; *crus*, crus commune; *c.sc. lat.*, ductus semicircularis lateralis; *c.sc. post.*, ductus semicircularis posterior; *c.sc. sup.*, ductus semicircularis superior or anterior; *cochlea*, ductus cochlearis; *coch. pouch*, cochlear anlage; *endolymph.*, appendix endolymphaticus; *sacc.*, sacculus; *sac. endol.*, saccus endolymphaticus; *sinus ut. lat.*, sinus utriculi lateralis; *utricle*, utricle.

pig embryos of 5 cm. the basal epithelium is thickened, the cells becoming highly columnar and the nuclei forming several layers. In later stages, 7 to 9 cm., inner and outer epithelial thickenings are differentiated, the boundary line between them being the future *spiral tunnel* (Fig. 386 A). At the free ends of the cells of the epithelial swellings there is formed a cuticular structure, the *membrana tectoria*, which appears first in embryos of 4 to 5 cm. The cells of the inner (axial) thickening give rise to the epithelium of the *spiral limbus*, to the cells lining the *internal spiral sulcus*, and to the *supporting cells* and *inner hair cells* of the spiral organ (Fig. 386 B, C). The outer epithelial thickening forms the *pillars of Corti*, the *outer hair cells*, and *supporting cells* of the spiral organ. Differentiation begins in the basal turn of the cochlea and proceeds toward the apex. The internal *spiral sulcus* is formed by the degeneration and metamorphosis of the cells of the inner epithelial thickening which is between the labium vestibulare and the spiral organ (Fig. 386 B, C). These cells become cuboidal, or flat, and line the spiral sulcus, while the *membrana tectoria* loses its attachment with them. The *membrana tectoria* becomes thickest over the spiral organ, and in full term fetuses is still attached to its outer cells (Fig. 386 C).

Hardesty (1915), on the contrary, asserts that the *membrana tectoria* is not attached permanently to the cells of the spiral organ.

From what is known of the development of the spiral organ in human embryos, it follows the same lines of development as described for the pig. It must develop relatively late, however, for, in the cochlear duct of a newborn child figured by Krause, the spiral sulcus and the spiral tunnel are not yet present.

The mesenchyme surrounding the labyrinth is differentiated into a fibrous membrane directly surrounding the epithelium, and into the perichondrium of the cartilage which develops about the whole internal ear. Between these two is a more open mucous tissue which largely disappears, leaving the *perilymph space*. The membranous labyrinth is thus suspended in the fluid of the perilymph space. The body labyrinth is produced by the conversion of the cartilage capsule into bone. In the case of the cochlea, large perilymph spaces form above and below the cochlear duct. The duct becomes triangular in section as its lateral wall remains attached to the bony labyrinth, while its inner angle is adherent to the modiolus. The upper perilymph space is formed first and is the *scala vestibuli*; the lower space is the *scala tympani*. The thin wall separating the cavity of the cochlear duct from that of the *scala vestibuli* is the *vestibular membrane* (of Reissner). Beneath the basal epithelium of the cochlear duct, a fibrous structure, the *basilar membrane*, is differentiated by the mesenchyme. The *modiolus* is not preformed as cartilage, but

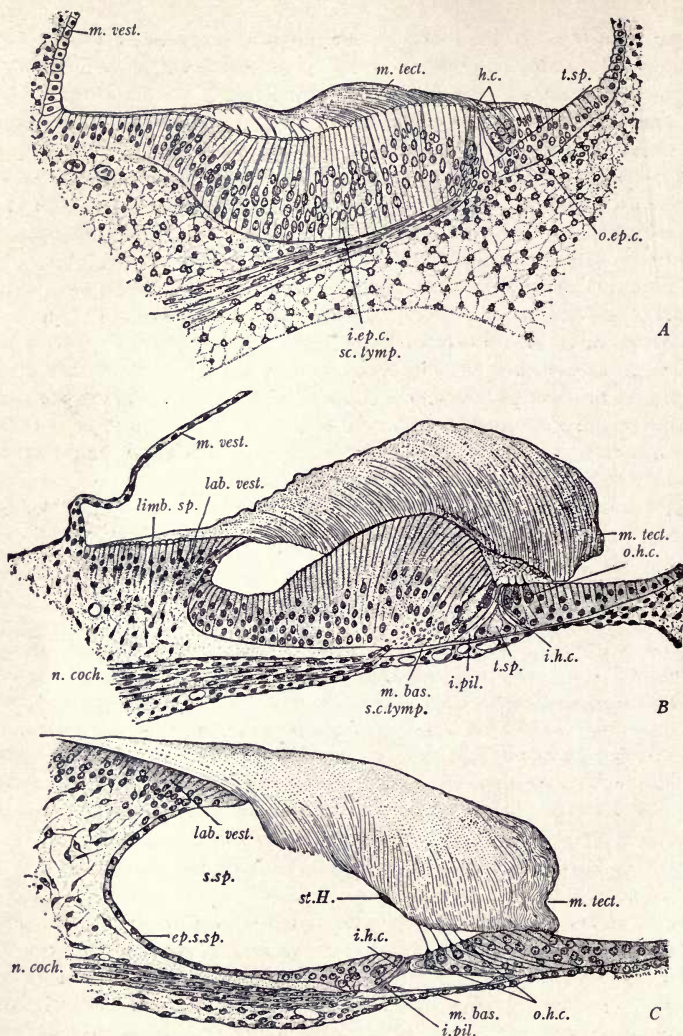


FIG. 386.—Three stages in the differentiation of the basal epithelium of the cochlear duct to form the spiral organ (of Corti), internal spiral sulcus and labium vestibulare. A, Section through the cochlear duct of an 8.5 cm. pig fetus ($\times 120$); B, from a 20 cm. fetus ($\times 140$); C, from a 30 cm. fetus (near term) ($\times 140$). *ep.s.sp.*, Epithelium of spiral sulcus; *h.c.*, hair cells; *i.ep.c.*, inner epithelial thickening; *i.h.c.*, inner hair cells; *i.pil.*, inner pillar of Corti; *lab. vest.*, labium vestibulare; *limb. sp.*, limbus spiralis; *m.bas.*, basilar membrane; *m.tect.*, membrana tectoria; *m.vest.*, vestibular membrane; *n.coch.*, cochlear division of acoustic nerve; *o.ep.c.*, outer epithelial thickening; *o.h.c.*, outer hair cells; *s.sp.*, sulcus spiralis; *sc.lymp.*, scala tympani; *st.H.*, stripe of Hensen; *t.sp.*, spiral tunnel.

is developed directly from the mesenchyme as a membrane bone. The development of the acoustic nerve has been described on p. 358 with the other cerebral nerves.

The Middle Ear.—The middle ear cavity is differentiated from the first pharyngeal pouch which appears in embryos of 3 mm. The pouch enlarges rapidly up to the seventh week, is flattened horizontally, and is in contact with the ectoderm (Fig. 168). During the latter part of the second month, in embryos of 24 mm., the wall of the tympanic cavity is constricted to form the *auditory* (Eustachian) *tube*. This canal lengthens and its lumen becomes slit-like during the fourth month. The tympanic cavity is surrounded by loose areolar connective tissue in which the auditory ossicles are developed and for a time are embedded. Even in the adult, the ossicles, muscles, and chorda tympani nerve retain a covering of mucous epithelium continuous with that lining the tympanic cavity. The pneumatic cells are formed at the close of fetal life.

The development of the *auditory ossicles* has been described by Broman (1899), with whose general conclusions most recent workers agree. The condensed mesenchyma of the first and second branchial arches gives rise to the ear ossicles.

The *malleus* and *incus* are differentiated from the dorsal end of the first arch (Fig. 387). The cartilaginous anlage of the malleus is continuous ventrally with Meckel's cartilage of the mandible. Between the malleus and incus is an intermediate disk of tissue, which later forms an articulation. When the malleus begins to ossify, it separates from Meckel's cartilage. The *incus* is early connected with the anlage of the *stapes*, and the connected portion becomes the *crus longum*. Between this and the stapes an articulation develops.

The *stapes* and Reichert's cartilage are derived from the *second branchial arch* (Fig. 387). The mesenchymal anlage of the stapes is perforated by the *stapedial artery*, and its cartilaginous anlage is ring-shaped. This form persists until the middle of the third month, when it assumes its adult structure and the stapedial artery disappears.

The muscle of the malleus, the *tensor tympani*, is derived from the first branchial arch; the *stapedial muscle* from the second arch. The further fact that these muscles are innervated by the trigeminal and facial nerves, which are the nerves of the first and second arches respectively, points toward a similar origin for the ear ossicles. These relations strengthen the general belief in a branchial arch origin.

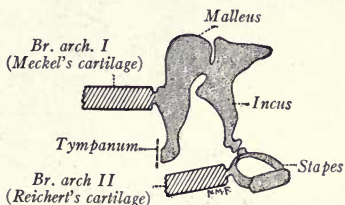


FIG. 387.—Diagram showing the branchial-arch origin of the auditory ossicles.

Fuchs (1905), studying rabbit embryos, on the contrary, concludes: (1) the stapes is derived from the capsule of the labyrinth; (2) the malleus and incus arise independently of the first branchial arch.

The External Ear.—The external ear is developed from the first ectodermal branchial groove and its adjoining tissue. The *auricle* arises from six elevations, which appear, three on the mandibular, and three on the hyoid arch (Fig. 388). Modern accounts of the transformation of these hillocks into the adult auricle agree in the main.

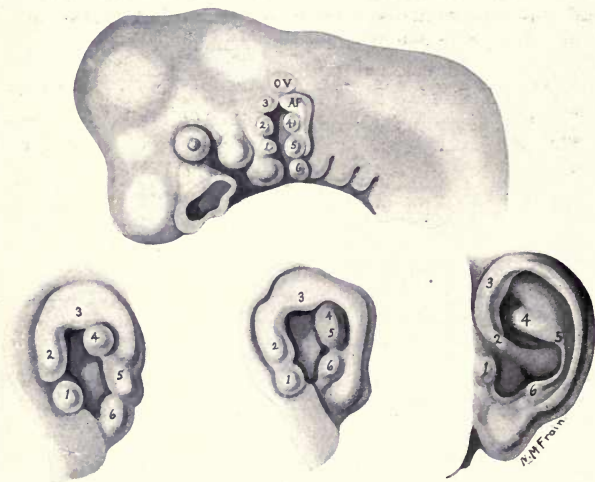


FIG. 388.—Stages in the development of the auricle. (Adapted in part after His.) A, 11 mm.; B, 13.6 mm.; C, 15 mm.; D, adult. 1, 2, 3, elevations on the mandibular arch; 4, 5, 6, elevations on the hyoid arch; af, auricular fold; ov, otic vesicle; 1, tragus; 2, 3, helix; 4, 5, antihelix; 6, antitragus.

Caudal to the hyoid anlagen a fold of the hyoid integument is formed, the *auricular fold*, or hyoid helix. A similar fold forms later, dorsal to the first branchial groove, and unites with the auricular fold to form with it the free margin of the auricle. The point of fusion of these two folds marks the position of the *satyr tubercle*, according to Schwalbe. *Darwin's tubercle* appears at about the middle of the margin of the free auricular fold, and corresponds to the apex of the auricle in lower mammals. The *tragus* is derived from mandibular hillock 1; the *helix* from mandibular hillocks 2 and 3; the *antihelix* from hyoid hillocks 4 and 5; the *antitragus* from hyoid hillock 6. The *lobule* represents the lower end of the auricular fold.

The *external auditory* meatus is formed as an ingrowth of the first branchial groove. In embryos of 12 to 15 mm. the wall of this groove is in contact dorsally with the entoderm of the first pharyngeal pouch. Later, however, this contact is lost, and, during the latter part of the second month according to Hammar, an ingrowth takes place from the ventral portion of the groove to form a funnel-shaped canal.

The lumen of this tube is temporarily closed during the fourth and fifth months, but later re-opens. During the third month a cellular plate at the extremity of the primary auditory meatus grows in and reaches the outer end of the tympanic cavity. During the seventh month a space is formed by the splitting of this plate and the secondary, inner portion of the external meatus is thus developed.

The *tympanic membrane* is formed by a thinning out of the mesodermal tissue in the region where the wall of the external auditory meatus abuts upon the wall of the tympanic cavity. Hence it is covered externally by ectodermal and internally by entodermal epithelium.

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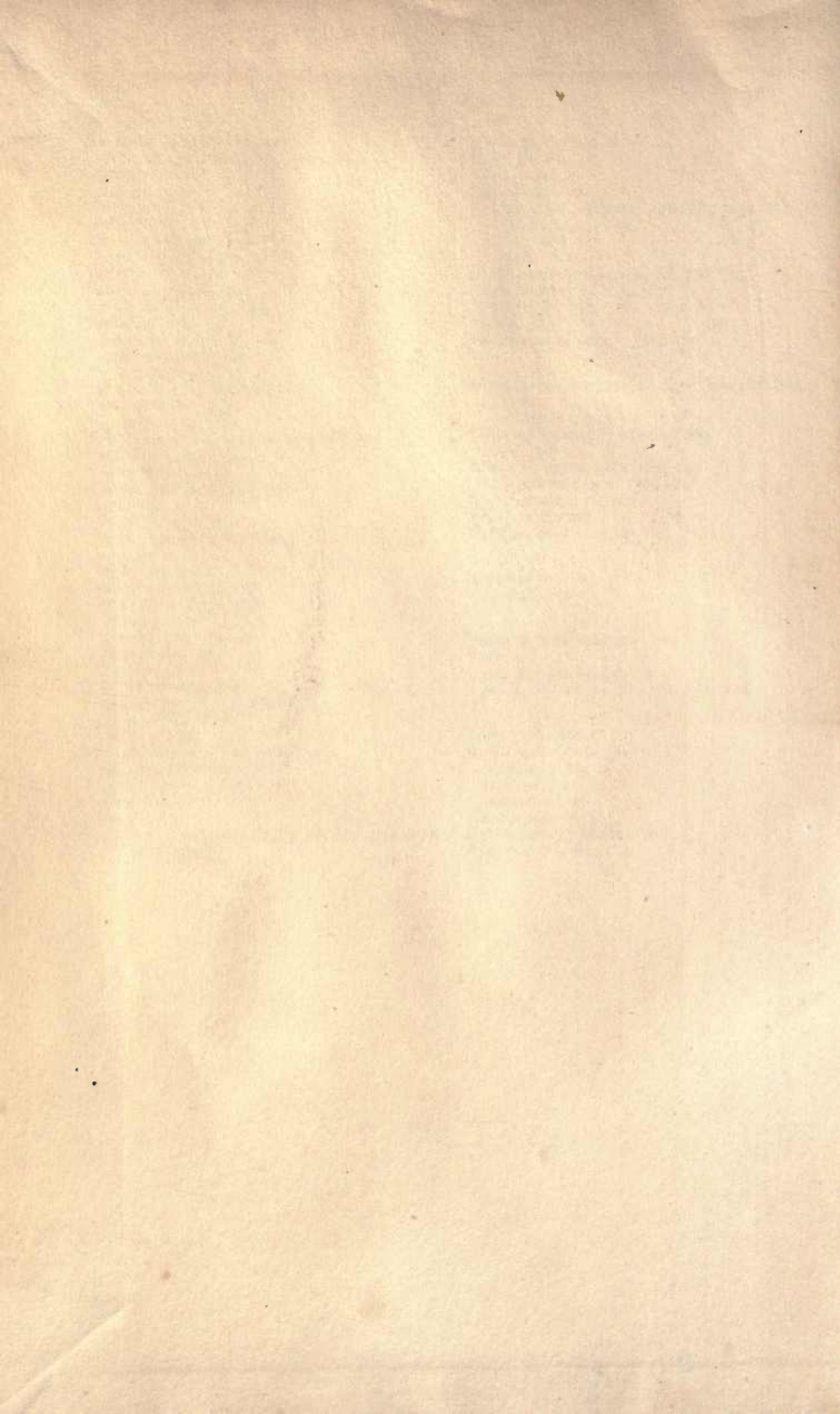
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